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FEBRUARY—1960
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1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

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*Green, J. R., & Sterlman, H. E.: Epileptic Seizures. Baltimore, Williams & Wilkins Company, 1956, p. 136.

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*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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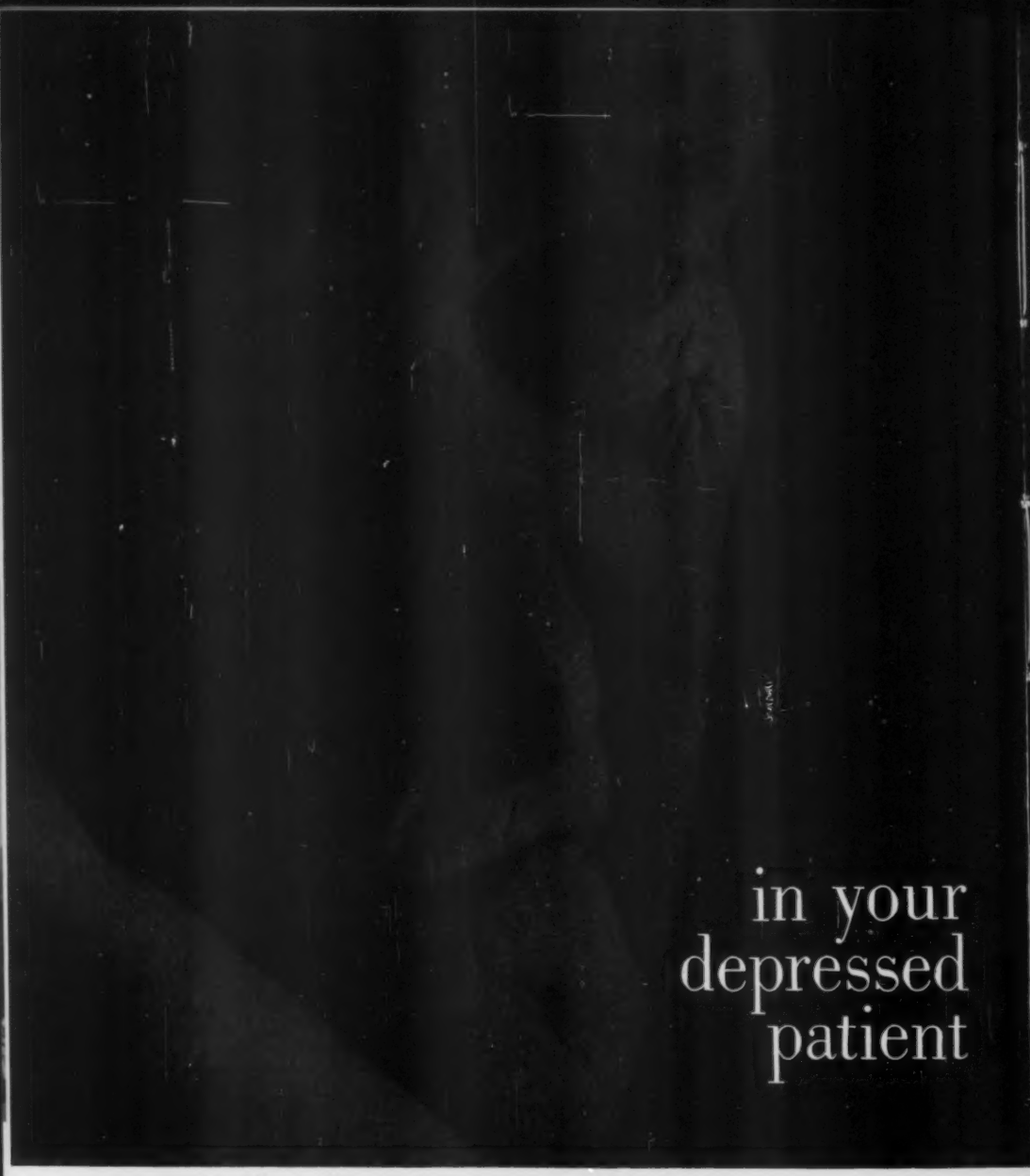

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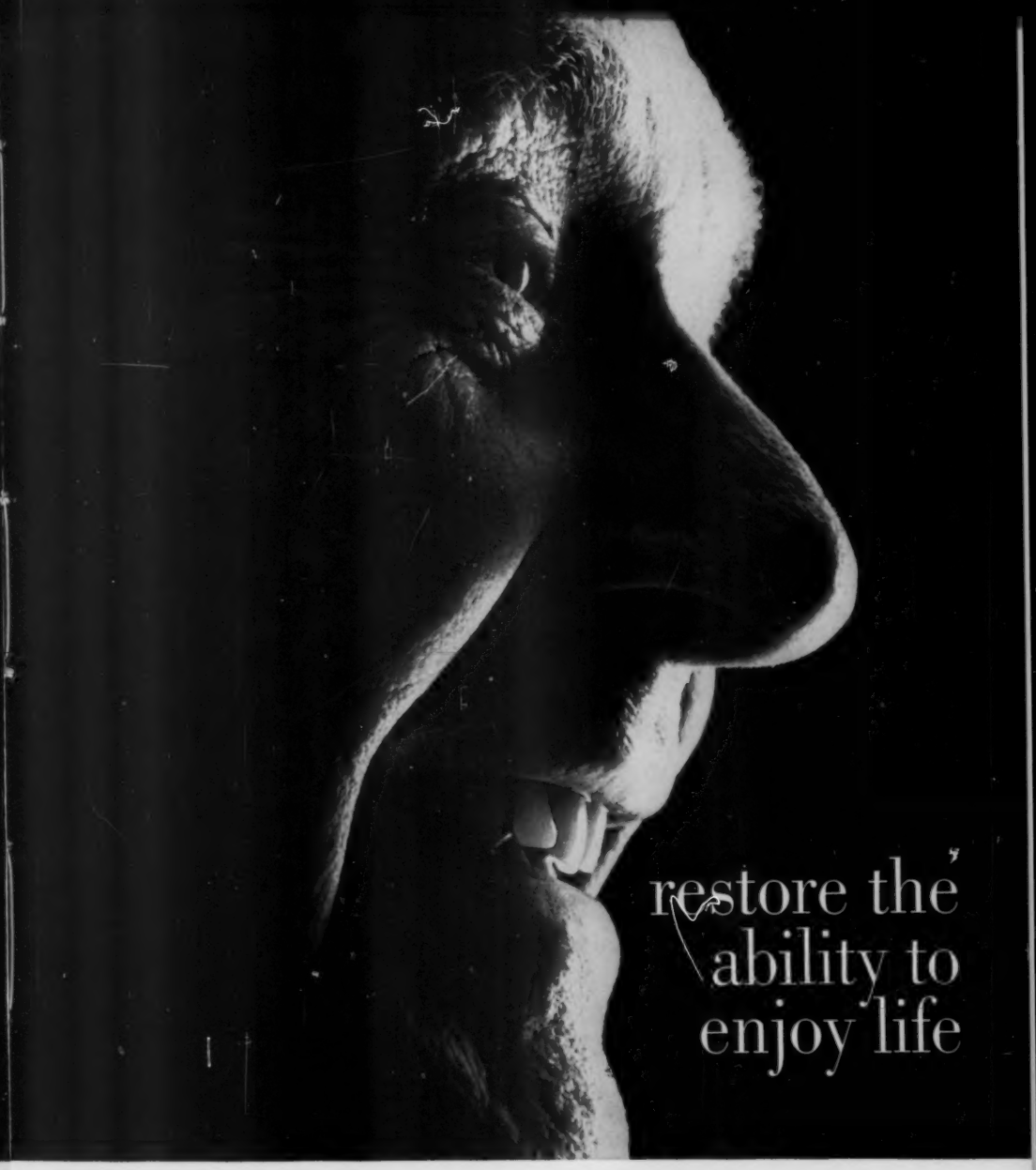

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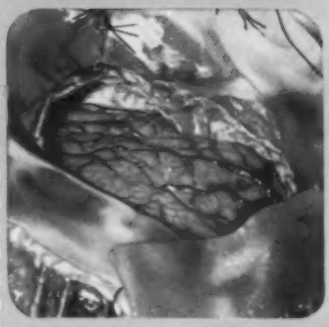

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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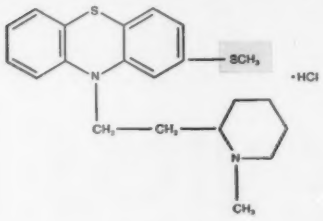

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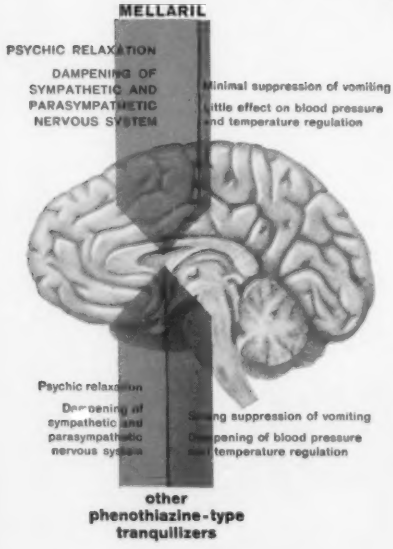

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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

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*Ayd, F. J., Jr.: New England J. Med. *261*:172, 1959.

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DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. Hence, caution should be exercised when combining CATRON with any other drugs such as tranquilizers, phenothiazines, the amphetamines, barbiturates, and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

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WARNING: Although pharmacologic evidence indicates that CATRON has a selectivity for the brain, it, as well as other monoamine oxidase inhibitors, may be associated with hepatitis. Because of the possibility of this life-threatening hepatitis, the following recommendations and precautions should be observed. If necessary, the patient should be hospitalized to expedite adherence to this regimen.

The Following Precautions Are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

SUPPLIED: CATRON is the original brand of phenelzine hydrochloride. It is supplied in tablets of 3 mg. and 6 mg., bottles of 50.

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Some characteristic features of the pathogenesis of myotonia

N. I. Grashchenkov, M.D.

MYOTONIA is rather a rare pathologic state, but the disease is so peculiar that its study is of great interest to both clinicians and physiologists.

There are 2 main forms of myotonia: Thomsen's disease (myotonia congenita) and atrophic myotonia (myotonia dystrophica).

We have succeded in showing that these are not 2 independent disease entities but forms of the same disease. Thorough examinations of patients with Thomsen's disease reveal a number of signs characteristic of atrophic myotonia: wasting of muscle groups, muscular weakness, lesions of the autonomic nervous system, and endocrine changes. Electrophysiologic, biochemical, and microscopic endocrinologic studies show changes of the same type in both cases; only quantitative, not qualitative, differences are observed, and they depend, in the main, on the severity of the patient's clinical condition. Our findings coincide with those obtained by a number of authors.[3,6,9,13,17,21,22,26,32,33]

The most striking phenomenon in the clinical picture of myotonia is myotonic spasm (stiffness) or myotonic reaction. This phenomenon is known to be a marked slowness of the muscle to relax after contraction and may be produced by voluntary contraction or electrical or mechanical stimuli. During repeated movement or stimulation, resistance to relaxation decreases or even completely disappears, but, after a period of rest, it may appear again.

In an analysis of the clinical manifestations of the myotonic phenomenon, the following characteristic features deserve emphasis.

1. The dynamic nature of the lesion and its connection with the functional activity of the motor neuron itself. Myotonic resistance to movement is manifested by intensive activity of the neuron and so too is the overcoming of the resistance.

2. The relation to the amount of effort exerted. A myotonic spasm occurs only in strong movements. Weak movements, a weak electric current, or mild mechanical stimuli do not produce the myotonic effect. In other words, myotonia occurs only at a certain level of muscular contraction.

The problem of the nature of the myotonic reaction has not so far been solved. In the rather extensive literature devoted to this problem, the following views may be distinguished:

1. The pathologic process is localized in the

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muscle. The advocates of this view[7,9,10,19,20,22] explain the myotonic phenomenon by the development of a state of contracture related to either hyperfunction of the sarcoplasm or biochemical change in the muscle.

2. Myotonia is conditioned by a reflex from the proprioreceptors, which are in a state of hyperexcitation.[1,5,12,16]

3. The myotonic reaction is conditioned by the development of parabiosis, according to Vvedensky.[31]

While studying the myotonic phenomenon by electromyography, the Russian scientists Rusinov and Chugunov[23,24] showed that the myotonic reaction is accompanied by action currents and that the appropriate motor nerve, during the myotonic response, shows no electrical activity. It follows that the neuromuscular junction is a focus of discharges. The authors point out that the development of such a focus at the junction can be understood in the light of Vvedensky's theory of parabiosis, and, on the basis of their studies, they speak of reduction of lability. Vasiliev[28] supported the views of these authors, holding that myotonia is a typical example of a prolonged manifestation of the second exaltation phase of parabiosis (with its characteristic rhythmic impulse) at the neuromuscular junction. I proceed to explain these terms.

Vvedensky and his numerous pupils have shown that study of the parabiotic area may reveal a regular alternation in electrical activity. The initial phase is electrically positive and is characterized by the electrotonic syndrome of a functional shift—excitability decreases, lability increases. In the second (exaltation) phase, which corresponds to the period of fluctuations of electrical potential during the transition from positivity to negativity, increase of excitability, which often exceeds the value of the initial level, is very characteristic. In this case, then, if not always, under certain conditions during the phase of restoration, the parabiotic area "becomes one in which spontaneous excitation occurs."[31] "An area of parabiosis in a nerve may become the source of steady impulses producing contractions of a tetanic or tonic nature in the innervated muscle."[28] In the closing phase, a steady, gradually increasing negative potential is established; the tendency to rhythmic activity is replaced by a constant focal excitation, and the electrotonic syndrome of functional shift is replaced by the cataelectrotonic syndrome (i. e., excitability and lability decrease). Here the phases of parabiosis, well-known in the U.S.S.R., take place in succession: the leveling, the paradoxical, and the inhibition.

In the process of development of parabiosis, a progressive decrease in the lability of the neuromuscular mechanisms may be observed.

By the expression "functional lability," Vvedensky meant the greater or lesser velocity of response which accompanies the physiologic activity of this mechanism.

Lability as a characteristic of the functional condition of nerve tissue reflects the velocity of reaction of tissue in the course of a single excitation; on the other hand, lability reveals the substrate's capacity in terms of single completed periods of excitation during a period of time.

The analysis of tetanic responses by rhythmic electrical stimulation at increasing frequencies is the most suitable method of clinical investigation, since it shows the characteristic features of the functional condition of the neuromuscular apparatus and gives us data concerning the threshold of intensity, time, and lability.

We know that tetanic responses depend a great deal on the lability of the neuromuscular substrate. This dependence enables us to judge its lability by the type of tetanic response and the conditions under which it appears.

Anochin and Slavutsky[2] were the first to suggest this method for clinical practice. The criteria adopted temporarily for the evaluation of the functional condition are: [1] the merging of single contractions into tetanus; [2] the frequency threshold for the first signs of the pessimum reaction of no response; and [3] the appearance of frank unresponsiveness, that is, of the pessimum. The unresponsive state is verified by a switch to low frequencies, when responses are always normal.

This method makes it possible to explore the lability of both the neuromuscular junction and the muscles themselves and to observe their dependence on various factors.

We adopted the method of rhythmic stimulation with an increasing range of frequencies in 20 myotonic patients. An electrotonic stim-

ulator of impulse currents according to Ritchi's system was used. The recording of the effect on the muscle was carried out by means of a special recording unit connected with a Marey capsule by an air transmission device. The tetanizing train of impulses was investigated at 1.5, 5, 10, 50, 70, 100, and 1,000 cycles per second, the duration of each impulse being 0.5 seconds and the strength of the current being 1.5 rheobase.

A normal tetanizing train of impulses was found in only 2 patients with a relatively mild form of Thomsen's myotonia. The other 18 patients showed various changes during the investigation. No fundamental differences in the tetanizing train were found among patients with Thomsen's myotonia and those with atrophic myotonia.

The pathologic state was shown partly by the occurrence of tetanus at low frequencies (5 and 10); this happened with 10 patients. In some cases, after muscular activity with temporary abolition of myotonic manifestations, these changes disappeared and the responses to 5 and 10 cycles per second were single contraction or there was a stepped curve in the response to 10 cycles per second, which is normal.

In some patients, a small increase in the strength of the current (in comparison with threshold values) produced a sudden increase in the amplitude of contractions. Increase in the strength of the current brought on the pessimum or no response reaction. These phenomena obviously point to shifts in the pattern of excitation, which changes in the course of the reaction.

In 16 patients, disturbances of a tetanic train were noted in the form of pessimum reactions at high frequencies. The threshold of this reaction in 7 patients has already been shown to begin at 50 to 70 cycles per second. As a rule, at high frequencies the pessimum or no response reaction was observed, mostly with transformation of the rhythm from continuous tetanus into a stepped curve. These phenomena may indicate low lability.

In 7 patients, a peculiar change in the shape of the tetanus curve was observed. After the initial rise, a more or less marked fall occurred, sometimes almost down to the initial value, followed by a second gradual rise. At higher frequencies, this fall after the initial rise was, as a rule, reduced and the curve became smooth and right angled. In some cases, however, higher frequencies produced tetanus—a pessimum reaction, often with transformation of the rhythm. Such a tetanic curve has been described and is known as veratrinoid; it may be observed during the investigation of muscles in animals poisoned by veratrine. It is remarkable that injections of veratrine into the muscle produce changes similar to those in the muscle of myotonic patients; the muscle shows the same motor reaction and response to mechanical stimuli, electrical currents, and injections of neostigmine and quinine, as if the muscle poisoned by veratrine emulated myotonic muscle.

Vvedensky described a similar form of tetanus at some phases in the development of parabiosis in strychnine poisoning.

Thus, on the grounds of the changes obtained, we are able to speak of decreased lability of the neuromuscular apparatus in the patients studied. The electromyographic data obtained by Rusinov and Chugunov[23,24] and Vasiliev[28] also confirm that myotonia is a typical example of a prolonged manifestation of the second exaltation phase of parabiosis, characterized by a rhythmic impulse at the myoneural junction.

As has been pointed out by Vasiliev, myotonia and myasthenia are typical manifestations of parabiosis. There is, however, a striking difference between the myasthenic and myotonic responses. The former is characterized by rapid inhibition of voluntary muscle contraction, the latter, on the contrary, by disappearance of the inhibition, that is, after exercise, muscle spasm in myotonic patients temporarily disappears. This difference can easily be explained by the theory of parabiosis. It is well known from laboratory studies that, in the initial stages of parabiosis, inhibition by impulses coming from elsewhere is abolished, as in myotonia; the advanced stage of parabiosis, on the contrary, is one of increased inhibition by these impulses, as in myasthenia.

The effect of deparabiosing and parabiosing factors on myotonic contracture lends support to these views.

As is known, in 1915-1917, Vinogradov[29] stated that application of the direct current

anode abolishes parabiotic manifestations, while application of the cathode aggravates them. Flekenstein and Richter[8] have shown that contracture of the rectus abdominis of the frog produced by acetylcholine, veratrine, or potassium chloride is abolished by anode polarization of the muscle.

Treatment by anodization is described by several authors. The effect of moderate warming and infrared rays is similar to that of the anode, while the effect of cooling and ultraviolet rays is similar to that of the cathode.

We have studied the influence of parabiosing and deparabiosing agents on the duration of the myotonic reaction. During the anodization of flexors and extensors, a distinct decrease in the myotonic reaction recurred in the upper and lower extremities. A similar effect was produced by a warm bath and infrared rays. A cold bath and chloric ether applied locally aggravated the reaction.

Thus, our findings fully confirm the presence of decreased lability in myotonic patients.

The reasons for this change in lability and for the parabiotic condition in the disease we are considering have so far remained obscure.

With the object of elucidating the biochemical factors producing this changed reaction, which is shown by increased excitability and decreased lability, we investigated a number of factors closely concerned with the process of excitation and muscle contraction—creatine-creatinine metabolism and blood phosphates and sugar, as well as blood potassium and calcium and urine, examined serially. We also investigated such biologically active substances as the acetylcholine-cholinesterase system, epinephrine, and the sympathins.

We succeeded in finding out that there was a pathologic abnormality in the process of phosphorylation (delay in the formation of creatine-phosphate, with accumulation of inorganic phosphorus and creatine) in most patients. Increase in the blood sugar ratio, delay in return of the sugar content to normal, and a curve with 2 peaks point to lesions in the regulatory mechanism of carbohydrate metabolism.

The study of potassium metabolism was of exceedingly great interest. It is well known that potassium ions play a considerable part in the physiology and pathology of neuromuscular activity. St. George[25] has shown the role of potassium ions in producing muscle contraction and relaxation.

In some myotonic patients, the potassium content of the blood serum is increased or is just within the upper limits of normal. However, the important thing is not the absolute amount of potassium but the pathologically increased sensitivity of neuromuscular tissue to potassium. We know that some substances, such as histamine and veratrine, as well as some muscle metabolites, can increase the sensitivity of tissues to potassium ions.

Oral administration of potassium salts has been shown to produce a great increase of myotonic manifestations in myotonic patients. A similar picture may be observed in myotonic goats after intraarterial administration of the substances mentioned.

On the other hand, a reduction in the potassium content by elimination of it from the body considerably improves the condition of the patient and decreases the myotonia.

ACTH treatment produces a regular improvement in the condition of the patient and, at the same time, a diminution of blood potassium, up to 14 to 15 mg. per cent in some patients. It is characteristic that this reduction of the blood potassium level is well tolerated by myotonic patients. Serial measurement of potassium in the urine in these patients shows a regular increase in its excretion, from the beginning of treatment. The potassium content of the urine is at its maximum up to the fourth or fifth day, this coinciding with the beginning of clinical improvement. On interruption of treatment, a great reduction in potassium excretion, up to 1 to 1.5 gr., is noted, which probably indicates an accumulation of potassium in the body up to the initial level.

The curative effect of ACTH and, to a certain extent, of cortisone, which, we found, is somewhat less effective in myotonia, is due, in the main, to the mineralocorticoid effect, that is, to the effect on the metabolism and excretion of potassium. This is supported by the fact that, at the same time as there is an increase in 17-ketosteroids and potassium excretion in the urine, there is an increase in corticosterone excretion. As is well known, corticosterone exerts a marked influence on mineral metabolism. The administration of other drugs, simi-

lar to cortisone but lacking in mineralocorticoid activity, such as Metacortin, was without effect on the severity of the myotonic manifestations. ACTH given to the same patients some time later produced its usual favorable effect.

We know the role of acetylcholine in the process of nerve excitation and the contraction of muscle. Excess of acetylcholine can change the reaction of the tissues and cause contracture. Numerous authors [4, 11, 14, 18, 30, 34] have pointed out that different doses of acetylcholine have different effects; small doses increase lability and make for excitation, while large doses diminish lability and may produce a parabiotic condition.

Apart from the effects of different doses, the degree to which the tissues are sensitive to acetylcholine plays a considerable part. Babsky and Kirillova[4] have shown that potassium ions intensify the effect of acetylcholine, while calcium ions diminish it.

The literature shows that the acetylcholine-cholinesterase ratio is changed, and the predominance of acetylcholine is noted. Some authors, basing their thought on clinical and biochemical grounds (estimation of acetylcholine and cholinesterase in muscle biopsies), conclude that, in myotonia, large amounts of acetylcholine occur and cholinesterase activity decreases.

There is also some evidence of increased sensitivity of the neuromuscular substrate to acetylcholine in myotonia. Brown and Harvey[5] found that intraarterial injection of acetylcholine into myotonic goats increased the contractile effect by 30, as compared with normal animals.

Because of the characteristic feature that it is rapidly destroyed by cholinesterases after the beginning of excitation, acetylcholine can rarely be detected in the blood.[15,27]

We have found free acetylcholine in 19 patients, sometimes in rather large amounts. Acetylcholine content has been found to be higher in patients with Thomsen's myotonia than in patients with atrophic myotonia, indicating the greater severity of the myotonic spasm in the former.

The investigation of acetylcholine in patients after muscular work that temporarily abolishes myotonic manifestations has revealed a considerable decrease in acetylcholine activity. During continuous investigation of acetylcholine during treatment, a gradual reduction of acetylcholine could be noted pari passu with clinical improvement. The administration of neostigmine, which intensifies acetylcholine activity, produced a distinct aggravation of the myotonic symptoms. This is an indirect confirmation of the involvement of acetylcholine in the physiopathology of the myotonic state.

In the estimation of cholinesterase (true and pseudocholinesterases) in blood, no gross disturbances were noted; the amount of the enzyme was found to be within the limits of normal. In some cases, a tendency to increase of cholinesterase activity after temporary abolition of myotonic manifestations was observed.

It follows from these findings that the most considerable changes took place in the potassium-acetylcholine system. There are some studies on acetylcholine in which its significance in the physiopathology of myotonia is emphasized.

We should like to emphasize once more that the sensitivity of the tissues and organs is of vital importance, not the absolute amounts of these substances. For instance, one and the same amount of acetylcholine will be too little for a myasthenic patient, too much for a myotonic patient.

Attention should be paid to the interaction of different agents in the body of a patient (for instance, the relationship between potassium and acetylcholine in myotonic patients). It is known that, under certain conditions, acetylcholine is able to increase both tissue sensibility to potassium and the permeability of membranes to potassium ions. Potassium, in its turn, intensifies the effect of acteylcholine by increasing sensitivity to it and liberates acetylcholine from the bound form; potassium also contributes to the synthesis of acetylcholine.

Thus, a peculiar kind of "vicious circle" may be observed: acetylcholine intensifies the effect of potassium, while potassium produces increased action by acetylcholine. For this reason, favorable conditions for appearance of a change in lability and reaction are established, for example, an ability to respond for a long time and repeatedly to any form of stimulation.

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Incidence of cerebral infarction associated with ruptured intracranial aneurysms

A study of 8 unoperated cases of anterior cerebral aneurysm

Sheila H. Birse, M.B., Ch.B., and Mary I. Tom, B.A., M.B.

THE CAUSE of death after rupture of a berry aneurysm has often been in doubt in cases in which the amount and position of the hemorrhage were inadequate to account for the fatality.

In an attempt to elucidate this problem, we have made a study of the brains of all patients with ruptured intracranial aneurysm received in this department over a period of eighteen months. From these, we have selected 8 patients with aneurysm of the anterior cerebral–anterior communicating complex who died from three days to four and a half weeks after the first rupture. Apart from diagnostic lumbar puncture and carotid arteriography, no surgical procedures had been undertaken in these patients. Hypothermia was used terminally in 1, and another was treated by this method for five days. The patients, 6 of whom were hypertensive, ranged in age from 37 to 78 years, with an average age of 58.

In instances of ruptured aneurysm, we have frequently confirmed Robertson's[1] observation of gross cerebral infarctions at post mortem, and these 8 brains have therefore been studied in detail to determine the extent, distribution, and possible etiology of such infarcts.

METHOD

At least 1 section of cerebral cortex and white matter was taken from the areas supplied by each anterior, middle, and posterior cerebral artery. In addition, a section from the basal ganglia in the distribution of one or both middle cerebral arteries was examined. These sections were made routinely whether or not there was visible or palpable evidence of softening. Sections also were made of the aneurysm, the left and right anterior cerebral arteries, and other arteries as seemed appropriate.

Paraffin sections were prepared and stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, and cresyl violet.

FINDINGS

The terminal event in 3 of the 8 cases was a rupture of the hemorrhage into the anterior horn of the lateral ventricle; 2 of these 2 and 1 other with asymmetric cerebral swelling were found to have secondary increased intracranial pressure hemorrhages in the brain stem.

Moderate or severe arteriosclerosis of the cerebral vessels was found in 2 cases and slight nodular arteriosclerosis in 5 others. In addition, 1 showed moderate arteriolosclerosis. All the aneurysms had the typical structure of berry aneurysms with absence of the media and internal elastic lamina; 3 contained recent and 2, agonal thrombus. In 1 instance, the thrombus extended into the anterior cerebral artery (Fig. 8), but in no other case were thrombi or emboli demonstrated in the major cerebral vessels or in their peripheral branches.

In some cases, the larger cerebral arteries appeared to be excessively contracted. This contraction was most severe in the anterior cerebral arteries in the immediate vicinity of the aneurysm (Fig. 7).

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Based on a paper read at the twentieth annual meeting of the American Academy of Neurological Surgery in Toronto, November 1958.

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DISTRIBUTION OF SOFTENINGS IN 8 CASES

Site	*Right*	*Left*
Anterior cerebral artery distribution	6 (2)	6 (3)
Middle cerebral artery distribution		
Basal	0	2
Cortical	4 (1)	6 (2)
Posterior cerebral artery distribution	2 (1)	4 (1)

Figures in parentheses indicate number of cases having grossly detectable softening.

The most conspicuous finding in brain tissue was the frequent occurrence of cerebral infarction. Softening over and above that around intracerebral hematomas was present in 7 of the 8 cases.

Softenings were found in the distribution of all the major cerebral arteries (see table). They were most extensive in the areas supplied by the parent vessel of the aneurysm, the anterior cerebral, but were present almost as frequently in the areas supplied by the middle cerebral arteries. Increased intracranial pressure with asymmetric cerebral swelling probably accounts for most of the softenings in the distribution of the posterior cerebral arteries. The figures in parentheses in the table show the incidence of macroscopic infarcts, which occurred in only 3 cases. The contrast in the figures is an indication of the striking number of infarcts that would have been missed if microscopic examination had not been made of sections from areas which, on gross inspection, did not appear to be softened.

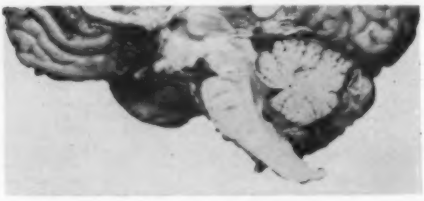

Fig. 1. (NP 263/57) Hemorrhagic disruption of the right septal area by rupture of anterior cerebral aneurysm

Fig. 2. (NP 263/57) Macroscopic softenings of three weeks' duration on the lateral surface and at the tip of the left frontal lobe

The septal area was destroyed in 7 of the 8 cases, bilaterally in 4 (Fig. 1). The destruction was obviously due to direct trauma by the hemorrhage from the adjacent aneurysm, rather than ischemic infarction. Of the 3 intracerebral ruptures, 2 tracked through the septal area.

Figures 2 and 3 demonstrate 2 of the types of softening encountered. Grossly visible softening of three weeks' duration is seen in the left frontal lobe in areas supplied by both the anterior and the middle cerebral arteries (Fig. 2). The microscopic infarcts were frequently focal and often multiple within 1 small area. Most often, these were confined to the cortex. The three-week softening in Figure 3, from the same case as Figure 2, was 1 of several found within a single microscopic section from the lateral aspect of the left parietal lobe. The block appeared normal on gross examination.

In addition, in several cases, more diffuse cortical infarcts of an early age were noted, in which the microscopic findings were edema of the tissue, and shrinkage with eosinophilia of the cytoplasm of the nerve cells without much evidence of destruction of the background tissue. These were too recent to be either visible or palpable but might, at a later stage, have been detectable on gross examination.

Another microscopic finding in 6 of the cases, including the 1 in which no infarction was demonstrated, was acute eosinophilic degeneration of occasional scattered nerve cells. This change was reminiscent of that seen in cases of anoxic anoxia and hypoglycemia.

Softenings of 2 or more histologic ages were noted in 4 of the cases. These corresponded fairly closely with episodes in the clinical histories suggestive of recurrent hemorrhage.

No correlation between the volume of subarachnoid hemorrhage and the degree of resul-

tant cerebral softening was found; 2 patients with massive subarachnoid hemorrhage had little or no softening, while 1 with very minor leakage had very extensive and widespread infarction.

Softening was demonstrated in both cases in which no arteriography had been performed. In 4 cases, surviving from five days to four and a half weeks from the time of the first hemorrhage, the softening was extensive. These were the 2 youngest and 2 older patients.

CASE REPORTS

Case 1. K. O'N. (NP 367/57) This 37-year-old man, who suffered frequent headaches and had a moderate labile hypertension for twelve years, had a subarachnoid hemorrhage twelve days before death and recurrent episodes with transient loss of consciousness on the following two days. Right carotid arteriography on the third day showed an aneurysm of the right anterior cerebral artery and lack of filling of the left anterior cerebral artery. His temperature fluctuated between 102 and 104° F. and the blood pressure, between 260/140 and 95/80. Four days before death, there was a rapid deterioration with development of paraplegia.

Postmortem examination revealed nephrosclerosis, atherosclerosis, and left ventricular hypertrophy, with slight early bronchopneumonia. The brain weighed 1,350 gm. Small, bilateral subdural hematomas were found over the vertex. The subarachnoid hemorrhage was massive. A pea-sized aneurysm of the right anterior cerebral–anterior communicating junction, which was filled with laminated clot, had ruptured into the right olfactory sulcus, also damaging the right septal area. The cortex compressed by this subarachnoid hematoma showed softening consistent with twelve days' duration (Fig. 4).

Softening could barely be palpated along the superomesial borders of the cerebral hemispheres and on the lateral surface of the left parietal lobe (Fig. 5). A small hemorrhagic softening was noted on the lateral aspect of the right occipital lobe. Histologically, these were of about eight to ten days' duration.

The microscopic sections revealed more widespread infarction than was suspected on gross examination. Those of the middle cerebral supply, in the right frontal and occipital lobes and the left caudate nucleus (Fig. 5), were also about eight to ten days in age.

Sections throughout the distribution of both anterior cerebral arteries showed more recent focal softenings involving mainly the cortex, more extensive on the right. It is of interest that, when the brain was subsequently reexamined after it had been in formalin for several weeks, these widespread, though focal, softenings had become palpable (Fig. 6).

Slight nodular atheroma of the internal carotid arteries and at the aneurysm site was seen. Both anterior cerebral arteries and the left middle cerebral artery were contracted (Fig. 7).

Fig. 3. (NP 263/57) Focal cortical infarct of three weeks' duration in the left parietal lobe. (Hematoxylin and eosin. × 35)

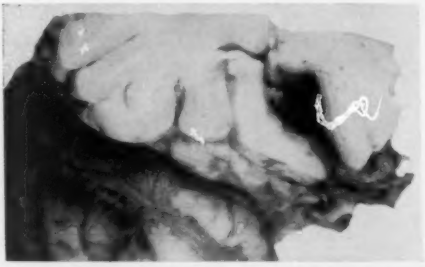

Fig. 4. *(Case 1)* Cortical disruption and softening due to compression by subarachnoid blood clot in the right olfactory sulcus

The laminated clot within the aneurysm sac was of several days' duration. A plug of platelet thrombus found in the right anterior cerebral artery at the neck of the aneurysm probably represented the tail of a retrograde thrombus, extending back into the artery from the aneurysm (Fig. 8). No emboli were found in any of the sections.

Possibilities that must be considered in explanation of this man's softenings are vascular spasm, the several rapid falls in blood pressure, and embolism from the thrombosed aneurysm.

In 1 of our 8 cases, however, embolism from the aneurysm can virtually be excluded.

Case 2. I. McK. (NP 488/57) This 42-year-old woman, whose previous blood pressure range was from 120/70 to 130/78, had leakage from her anterior communicating aneurysm over a period of about twenty-four hours one week before her death. She was admitted unconscious in a state of decerebrate rigidity, with a blood pressure of

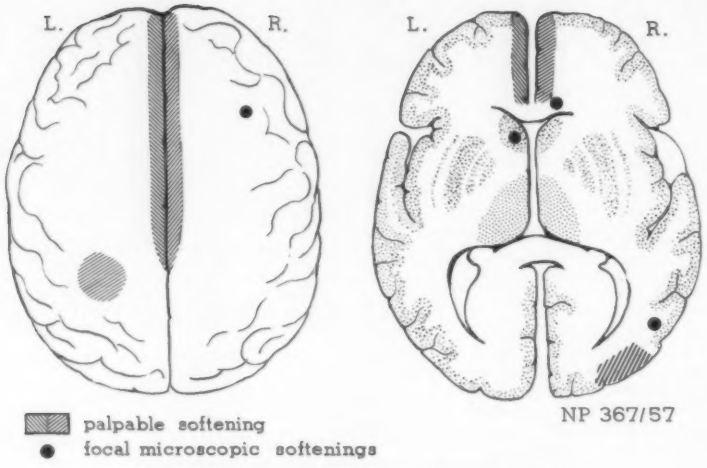

Fig. 5. *(Case 1)* Diagrammatic representation of macroscopic and microscopic cerebral infarction

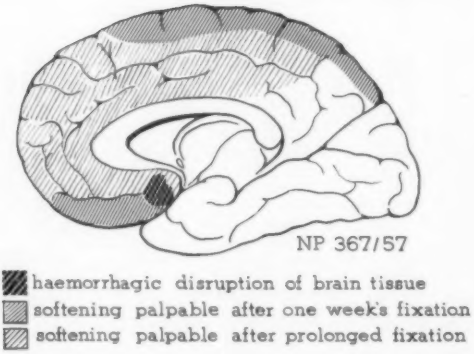
NP 367/57
haemorrhagic disruption of brain tissue
softening palpable after one week's fixation
softening palpable after prolonged fixation

Fig. 6. *(Case 1)* Diagrammatic representation of palpable softening of the mesial aspect of the right cerebral hemisphere

100/54. The blood pressure remained at this level or lower until her death six days later. During this time, she showed a gradual improvement under treatment by hypothermia but died suddenly, about twenty-four hours after hypothermia was discontinued.

Postmortem examination was limited to the brain, which weighed 1,230 gm. and was edematous. The left occipital lobe was swollen. There was a trace of left subdural hemorrhage. The subarachnoid blood was scanty and confined to the frontal poles.

Figure 9 shows the extent of the softenings palpated on gross examination after several days' fixation in formalin and again at a much later date. Here, too, unsuspected focal cortical softenings were found on microscopy. Scattered necrosis of nerve cells also was occasionally seen. Infarcts were found in 3 out of 5 sections of cortex from the area of supply of the right middle cerebral artery.

No arteriosclerosis was seen, except at the aneurysm site. The large berry aneurysm was empty. The anterior cerebral arteries were contracted. The right anterior cerebral artery proximal to the anterior communicating had not filled on arteriography and was found at autopsy to be threadlike. The posterior communicating artery was also inadequate (Fig. 10). Although a circle of Willis was present, no flow of blood from the aneurysm sac to the right middle cerebral artery was possible through either the right anterior cerebral or the right posterior communicating artery. Thus, the right middle cerebral infarcts cannot have been caused by embolism from the aneurysm.

Brief mention might be made of 7 cases of internal carotid or middle cerebral aneurysm surviving more than twenty-four hours. In 5 of these, the neck of the bleeding aneurysm had been clipped. Remote softening was demonstrated in 5 of the 7 cases. In the 1 unoperated case, the aneurysm sac had been completely sheared off the right internal carotid artery. Carotid arteriograms, repeated after the development of left hemiplegia five days after admission and three days before death, showed a diminution in the caliber of the

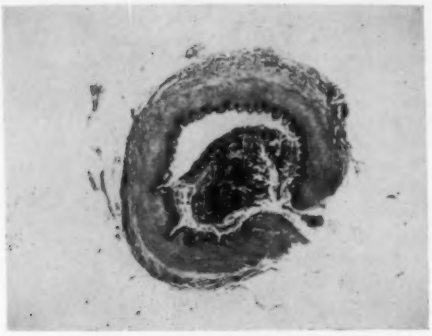

Fig. 7. *(Case 1)* Marked contraction of the right anterior cerebral artery immediately proximal to the anterior communicating artery. (Phosphotungstic acid hematoxylin. × 17)

Fig. 8. *(Case 1)* Platelet thrombus just within the right anterior cerebral artery at the neck of the aneurysm. (Phosphotungstic acid hematoxylin. × 15)

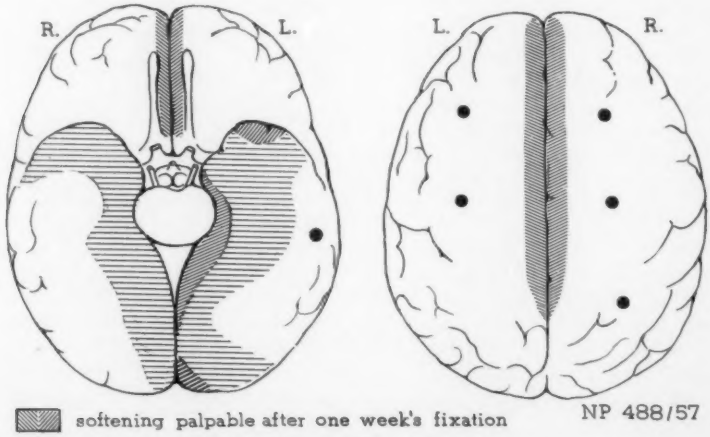

Fig. 9. *(Case 2)* Diagrammatic representation of macroscopic and microscopic cerebral infarction

right internal carotid artery and its branches. This brain showed softening in all regions of the cerebral hemispheres, all of about one to three days' duration in histologic appearance.

COMMENT

This study has corroborated Robertson's belief that cerebral infarction occurs commonly

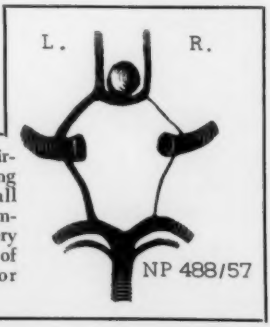

Fig. 10 *(Case 2)* Circle of Willis showing anomalously small right posterior communicating artery and proximal part of the right anterior cerebral artery.

after rupture of an intracranial aneurysm. The most outstanding finding was the high incidence of focal infarction found on microscopic examination of tissue appearing grossly normal or, at most, edematous. As far as we are aware, these microscopic infarcts have not previously been recorded, with the possible exception of Case 12 in Frankel and Alpers'[2] paper, in which the authors do not indicate whether they found their microscopic cortical infarcts in grossly normal tissue as well as in the area of macroscopic softening.

Reexamination of the brain after prolonged fixation demonstrated previously unsuspected cerebral infarction in several cases.

It is felt that widespread cerebral complications played a major part in causing death in at least 2 of the cases, in addition to giving rise to some of the clinical neurologic signs and symptoms.

The etiology of remote softening associated with rupture of a berry aneurysm remains obscure. In each case, various possibilities were considered. These included thrombosis and embolism, pressure from hematomas, cerebrovascular disease, arterial spasm, and hypotension. No one factor common to all the cases was found.

SUMMARY

Detailed examination has been made of the brains of 8 patients dying, without operative interference, as a result of rupture of a berry aneurysm of the anterior cerebral–anterior communicating complex; 5 of the aneurysms contained recent or agonal thrombi.

Cerebral infarction related to the hemorrhage from the aneurysm was detected in 7 of the 8 cases but was grossly demonstrated in only 3. In all 7 cases, softening was present in the areas of supply of the parent vessel of the aneurysm. Remote infarction also was found in 6 cases.

Of the 8 cases, 6 showed eosinophilia of the cytoplasm of scattered cortical nerve cells, suggestive of anoxic anoxia.

Gross and microscopic examination failed to reveal the cause of the cerebral infarcts. In 1 case, it was possible to exclude embolism from the aneurysm sac as a causative factor in some of the remote lesions.

A similar incidence of remote softening was found in 6 surgically treated cases of berry aneurysm and 1 unoperated case of an aneurysm of the internal carotid artery.

The authors wish to thank Dr. E. A. Linell of the Division of Neuropathology, University of Toronto, and Dr. E. H. Botterell of the Neurosurgical Division, Toronto General Hospital, for their encouragement and advice. We are indebted to Mrs. D. Elliott, Mrs. J. Gallacher, and Miss M. Budd of the Division of Neuropathology for their careful preparation of the extensive histologic material, to Miss C. Bell for her secretarial assistance, and to Miss E. Blackstock, Department of Art as Applied to Medicine, for the drawings.

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Effect of serotonin in migraine patients

Robert W. Kimball, M.D., Arnold P. Friedman, M.D.,
and Edward Vallejo, M.D.

LITTLE is known of the factors that predispose to migraine or the biochemical events that initiate the disturbances characteristic of this condition. Earlier studies by Marcussen and Wolff[1] have shown that an initial phase of vasoconstriction is responsible for the prodromal symptoms, while the pain follows a marked distention of cranial vessels that are temporarily hypotonic. They also have presented certain evidence which presumably indicates that a pain threshold–lowering substance renders the distention of the large arteries painful.[2] However, alteration in tone, lumen, and pain threshold of the arteries alone cannot explain the complex symptomatology of the migraine attack.

Jimenez Diaz and associates[3] have indicated that, during the migraine attack, there is a release of a substance more stable than acetylcholine, which they term S.A.C. acetylcholine-like substance. They also conclude that the normal choline acetylate system is different in these patients. Kunkle[4] also relates this multisystem disturbance to a preponderance of parasympathetic nervous activity as manifested by a release of acetylcholine. An acetylcholine-like substance has been detected in cerebrospinal fluid during some intracranial vascular headaches of migraine type. These and other studies cast light on the nature of the pathophysiology of migraine, yet the primary event in the migraine attack remains undetermined. The effects of serotonin (5-hydroxytryptamine—HT) suggest themselves as a means of gaining further understanding of migraine.

The present study undertakes to determine the effects—clinically, physiologically, and biochemically—of serotonin and its precursor, 5-hydroxytryptophane (HTP), on patients with migraine. The physiologic significance of HT is implied by its potency in the central nervous system, gastrointestinal tract, cardiovascular system, and blood. The cardiovascular phenomena associated with HT excess are particularly interesting, in that its ability to produce vasoconstriction in some instances, and in some instances vasodilation, raises the possibility that this or a similar substance is the trigger, or part of the trigger mechanism, in patients with vascular headaches, that is, migraine. The nervous, cardiovascular, gastrointestinal, and renal effects of HT all have their counterparts in the migraine syndrome. It has been stated by other observers that exogenous HT can elicit an attack of migraine,[5] and observations with a monoamine oxidase inhibitor have been interpreted to indicate that HT aggravates the symptoms of migraine.[6] Wolff and associates[7] have reported that, in 3 cases, temporal perivascular-injected HT induced effects similar to clinical migraine. This and other clinical studies suggest that a biochemical lesion of fundamental importance exists in migraine.

MATERIALS AND METHODS

Patients used in this study were a group of 18 females and 17 males between the ages of 24 and 70, all of whom meet our previous criteria for migraine[8] and are otherwise in good health. They were all studied at the Montefiore Hospital Headache Unit. Complete physical and neurologic examination was done on each patient.

In each subject, the electroencephalogram and pulse wave were recorded before and after intravenous HT and HTP; 5 mg. of HT was given over a five-minute period, and vital signs were observed during injection. The dose of

From the Headache Unit, Montefiore Hospital, New York City.

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HTP varied from 10 to 20 mg. and was given in a period of one to two minutes. All experiments were controlled with saline injection by means of a double-blind technic.

Having received the HT and HTP, 25 patients received phenelzine in doses of 75 mg. per day for one week, in order to increase endogenous HT. Plasma levels of HT were determined in 3 patients after this treatment and in 3 patients with spontaneous headache; these levels were compared to those found in patients without headache and without treatment.

After a week's treatment with phenelzine, 3 subjects received BOL (2-bromo-LSD) in a single intravenous dose of 1.5 mg., while 10 received 1.25 mg. per day for one week.

After phenelzine, 9 patients received 25 mg. of chlorpromazine intravenously; 15 subjects received 2.5 mg. of reserpine intramuscularly. Of these, 5 were receiving phenelzine at the time.

Injections of 0.1 mg. HT were given to 10 subjects near the temporal artery after induction of 3° of temperature elevation by means of hot water immersion.

RESULTS

The symptoms produced by intravenous HT in the migraine subjects were faintness, flushing, and paresthesias. No consistent significant change in pulse, respiration, or blood pressure was observed. Transient dyspnea was observed in all but 4 patients. All symptoms were transient and were more marked in the female than in the male patients. In 4 of the males, no symptoms or objective changes were noted. In no instance did a headache follow intravenous HT or the paratemporal infiltration of HT. Intravenous HTP in doses as high as 16 mg. produced no symptoms whatever.

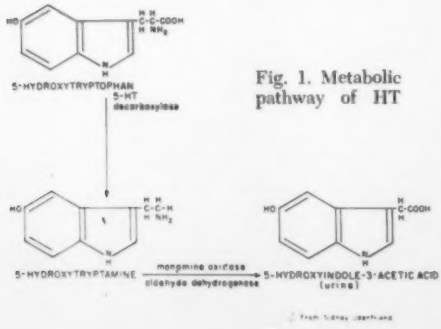

Fig. 1. Metabolic pathway of HT

Electroencephalograms in all subjects were normal, and no change followed intravenous HT or HTP. No characteristic change in amplitude or contour of pulse tracings was observed with either HT or HTP. No significant change in plasma HT was found in the 3 patients with spontaneous headache. An increase in plasma HT was seen in patients receiving the monoamine oxidase inhibitor, phenelzine. There were no findings to indicate deviation from the usual metabolism of HT (Fig. 1).

In all patients but 1 receiving phenelzine over one-week periods, headaches decreased markedly in severity or frequency. BOL following phenelzine produced no further change in frequency and severity of headaches. Single 25-mg. intravenous doses of chlorpromazine in 9 phenelzine-primed patients produced no effect but somnolence; 10 patients received BOL for periods of one week with a marked improvement of headaches. In 5 patients, spontaneous headaches were relieved with 5 mg. of HT intravenously, and, in 3 patients, they were relieved with HTP. HTP also relieved reserpine-induced headaches in 5 cases. Reserpine produced a migraine-like syndrome in 10 patients.

DISCUSSION

Headache (migraine) is produced in migrainous patients with intramuscular injection of 2.5 mg. of reserpine. Headache is not produced by chlorpromazine, another tranquilizer that presumably has a different mode of action. Chlorpromazine does have some sympatholytic effect, which might result in a reduced blood vessel tone.

When reserpine is administered, vasodilation is observed. This could be due to the release of and action of HT or could be a parasympathomimetic effect. In animals, when HT is infused intravenously rapidly, the blood pressure will rise, and when HT is infused slowly or when HTP is given, there is a fall in blood pressure. Since the parasympathomimetic effects that follow reserpine are known to continue on chronic dosage, it would be improbable that they are a direct action of HT. These effects could be due to an increase in acetyl-

choline activity or a relative overplay of acetylcholine based on the reduction of such sympathetic substances as epinephrine, norepinephrine, and HT.

The present studies show that HT and HTP given intravenously do not produce migraine. This would further argue that the reserpine migraine effect is not due to an action of HT. The raising of the endogenous level of HT by the use of a monoamine oxidase inhibitor, phenelzine in this study, does not produce migraine. The administration of BOL does not invoke or aggravate migraine. It is at least of passing interest that headache has not been reported with the carcinoid syndrome.[9–11]

Rather, HT and/or its precursor HTP, given intravenously, relieve migraine and also relieve the migraine model (reserpine) headache. Also, phenelzine reduces the incidence and severity of migraine attacks. The same is true of BOL.

Virtually no drug has a pure action, and the effects seen in these experiments could be nonspecific ones. However, the substances are all sufficiently closely related chemically so as to share certain pharmacologic actions and certainly to share the ability to attach themselves to the same receptor sites (Fig. 1). An example of this multiplicity of action is phenelzine, which has, on intravenous injection, a sympathomimetic effect similar to such drugs as norepinephrine or amphetamine (also useful in migraine). Phenelzine also produces a sympatholytic-like effect resulting in postural hypotension. At the same time, the circulating and brain HT increases, and we get a psychic-energizer action, presumably due to the affinity of this substance for monoamine oxidase and the resultant blocking of these receptor sites.

From the current therapy in migraine, we see this same difficulty of multiplicity of effects, since the ergot derivatives are both vasoconstrictor, presumably through a direct muscle action, and adrenolytic or sympatholytic, causing a reversal of epinephrine effects.

It is also possible that more mechanisms than 1 are involved in the provoking of an individual attack and therefore are available as an approach for the treatment of an attack. But, if we assume that the headache produced by reserpine is due to a reduction in HT at a

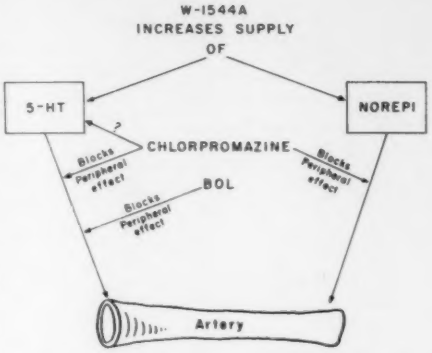

Fig. 2. Schematic representation of blocking agents and their influence on HT and norepinephrine

vascular site, the effect of HT and its precursor HTP in replacing this would follow and headache relief could be expected. The effect of phenelzine would also be explained, as the monoamine oxidase blockade resulted in a protection of endogenous HT.

One would have some difficulty in explaining the role of BOL on this basis except that, at the site which we may be discussing, it may have the same effect as HT. The anti-HT effect of BOL is usually demonstrated with blood vessels in vitro, and it need not follow that the effect being observed on contraction and relaxation in such a system is the effect that we are studying in migraine. It is highly unlikely that BOL is a pure pharmacologic entity and that it does not have some of the same actions that both phenelzine and HT show (Fig. 2).

This situation is further complicated by the possibility that all of these substances are acting in the central nervous system and not at the vessel site, since they are all known to have such effects. Even HTP has been shown to be capable of producing hallucinations when administered in large quantities.[12]

The ameliorating effect attending increased endogenous serotonin is unaffected by the peripheral blocking action of BOL. This observation can be interpreted as evidence against the peripheral site. That the serotonin effect and release of acteylcholine are independent events is suggested by the relief of

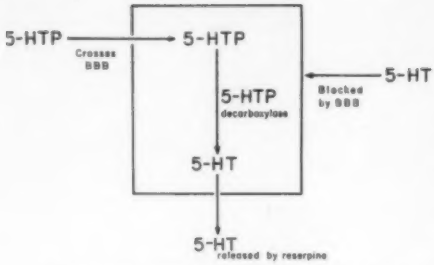

Fig. 3. Diagram depicting HT and 5-HTP and their penetrability of blood-brain barrier (BBB)

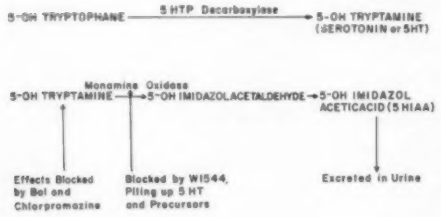

Fig. 4. Effect of phenelzine (W-1544) on HT metabolism

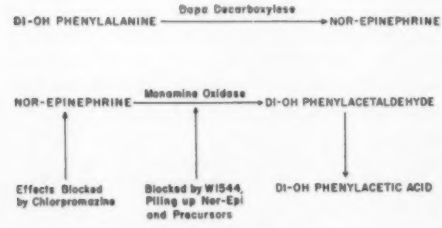

Fig. 5. Effect of phenelzine (W-1544) on norepinephrine metabolism

headache by HTP without interrupting pronounced vagal effects, for instance flushing.

Separation of peripheral and central effects depends on the impermeability of blood-brain barrier to HT and the permeability to HTP. The mechanism whereby HT exerts its central nervous system influence has been partially adumbrated by the study of reserpine's effect on the central nervous system. Reserpine depletes the brain of serotonin and produces certain pharmacologic effects, for example, prolongation of sedation. Whether these effects of reserpine are caused by free serotonin or by its absence from the brain cells is not certain. The explanation that reserpine's effects are due to free serotonin assumes that small amounts of serotonin cross the blood-brain barrier.[13] On this point there is a degree of uncertainty. That some serotonin could cross the blood-brain barrier offers no hardship to the interpretation of our results and, in fact, could account for the improvement in spontaneous headache observed to follow intravenous HT (Fig. 3).

While there is evidence to support the view that depletion of HT and migraine are related, difficulty arises in attributing the ameliorating effects of phenelzine solely to the attendant rise in HT. The effect of the phenelzine molecule itself has been neglected, and further observations are necessary in order to determine the effect of amines, other than HT, that accumulate as a result of monoamine oxidase inhibition (Figs. 4 and 5).

A number of points remain to be elucidated, among which is the peripheral effect of reserpine. In the absence of strong supporting evidence for peripheral action of HT in migraine, the reproducibility of migraine by HT depletion can be considered a useful hypothesis for further study of the migraine problem.

SUMMARY

1. Neither HT nor HTP has induced migraine by intravenous administration in 35 cases. Subcutaneous paratemporal arterial injections of HT in 25 cases failed to produce symptoms of migraine.

2. Increase in endogenous serotonin by means of phenelzine, a monoamine oxidase inhibitor, did not provoke migraine.

3. Peripheral block of serotomin by BOL has not provoked migraine.

4. HT and HTP did not produce electroencephalographic changes in 35 cases of migraine with normal tracings.

5. Reserpine (2.5 mg. intramuscularly) induced typical migraine headache in 9 of 10 patients by a mechanism remaining to be clarified.

6. Phenelzine, a monoamine oxidase inhibitor, given over a short period of time in this

series, has markedly reduced the frequency and severity of migraine.

7. BOL given over a short period of time in this series has markedly reduced the frequency and severity of migraine.

8. HT has abolished spontaneous migraine headaches. HTP has abolished both spontaneous migraine and reserpine-induced headaches.

9. In 3 instances of spontaneous migraine, the plasma level of HT was found to be not remarkably altered.

10. Possible mechanisms of migraine and the role of serotonin are discussed.

The authors wish to thank Drs. William Govier, Saul Korey, and Joseph White for their advice and suggestions and Mrs. Elsie Kathman for her assistance in carrying out this research project.

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Circulation of the spinal cord studied by autoradiography

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THE EFFECT of ischemia on the spinal cord has been studied by many workers. In 1669, Niels Stensen,[1] followed by Dubois-Reymond[2] and others,[3–6] ligated the abdominal aorta in the rabbit and studied the effect of this operation on the spinal cord. After ligation of the abdominal aorta for thirty to forty-five minutes, Ehrlich and Brieger[6] noted physiologic recovery in a short time. Ligation for one hour or more produced persistent flaccid paralysis. Some of their animals remained alive for six and one-half weeks, and, in these, advanced destruction was noted in the gray matter of the cord. The spinal ganglia and dorsal roots appeared normal, while the ventral roots were completely replaced with connective tissue. The posterior column appeared normal with the exception of a small area near the gray commissure. The anterolateral white column showed degeneration, except for the pyramidal and spinocerebellar tracts. They believed that the degeneration noted was confined to short tracts. Singer[7] confirmed their results.

Spronck[8] found that ligation of the aorta for ten minutes produced no changes, while ligation for thirty minutes produced inconstant results. His histologic findings agreed with those of Ehrlich and Brieger. Herter[9] concluded that compression of the abdominal aorta lasting for less than forty-five minutes produced a paralysis that rapidly disappeared and that compression for more than an hour was necessary to produce a permanent paralysis. He found no disturbance in sensation.

Observations on the ischemic changes of the neurons of the spinal cord following occlusion of the abdominal aorta, either through a surgical procedure or by external compression against the spinal column, were made during the nineteenth century by many investigators.[10–18] De Buck and de Moor[19] extensively reviewed all studies on this subject up to 1900, adding their own experiments with the rabbit. They concluded that thirty minutes of ischemia produced by ligation of the abdominal aorta would produce total destruction of the neurons in the anterior horn. They noted that a period of from one and one-half to two hours must elapse after reestablishment of circulation before any histologic evidence of ischemia would appear. Tureen[20] ligated the thoracic aorta in cats immediately below the aorta arch and concluded that less than fifteen minutes' ligation is compatible with physiologic and histologic recovery of the anterior horn cells. He found no histologic changes in animals killed less than seven hours after the compression, while animals that were sacrificed later, up to five days following ligation of the aorta, revealed a diffuse chromatolysis involving almost all the neurons in the anterior horn of the affected portion of the spinal cord, but, after six days, no histologic changes were noted. Paraplegia was observed before detectable histologic changes were apparent, and the neurons showed the greatest degree of cytologic change at a time when the paralysis had disappeared.

Tureen[21] also noted that periods of partial ischemia result in excessive increase in minerals within the nerve cell, which persist in a disorganized manner for about one week after ischemia. Reorganization of the mineral structure commenced within one week and was not

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complete for a month. Periods of total ischemia resulted in loss of minerals. Though Tureen failed to produce ischemic changes in the spinal cord with ligation of the abdominal aorta at the level of the left renal artery in the cat, Häggquist[22] found that, in the rabbit, large motor cells and their axonal processes were most rapidly destroyed after ischemia for fifteen minutes by external compression of the abdominal aorta.

Rexed,[23] using rabbits and the methods devolped by Häggquist, measured the electrical irritability of the paralyzed muscle. No permanent effects on function were obtained after ligation for less than fifteen minutes, while, after ligation for fifteen to twenty-five minutes, a persistent paralysis appeared in some animals. The affected muscles showed a partial reaction of degeneration at times after fifteen to twenty-five minutes' ligation. However, after a longer period, a flaccid paralysis was obtained and the affected muscles of these animals atrophied quickly and showed a total reaction of degeneration. Hochberg and Hyden[24] compressed the abdominal aorta of rabbits using Häggquist's clamp. These authors found that the neurologic deficit resulting from a fifteen-minute ligation was reversible. Occlusion of the abdominal aorta for twenty-five minutes produced paralysis in the hind limbs, which was accompanied by a striking decrease in the nucleoprotein contents of the cytoplasm of the motor cells, noted within four hours after the period of ligation. The majority of the anterior horn cells underwent degeneration. The nucleic acids and proteins in both the nuclear apparatus and the cytoplasm disappeared at the onset of paralysis and were not replaced.

Krogh,[25,26] also using Häggquist's method in the rabbit, reported that, after ten to thirty minutes' occlusion, the nerve cells in the central part of the anterior horn were more severely damaged than those in the peripheral regions of the anterior horn. He believed that this was due to differences in vascularization. Gelfan and Tarlov,[27] on the basis of recordings from the spinal cord after thoracic aorta ligation, concluded that the motor neurons are more sensitive to anoxia than the interneurons and that the interneurons are more sensitive than the fibers of the dorsal columns. They concluded also that complete recovery was possible with less than thirty minutes of anoxia but that recovery was incomplete if aorta ligation continued for a longer period. Twenty minutes of ligation produced loss of function of all afferents.

Yoss[28] produced experimental vascular lesions of the spinal cord in the monkey. In his experiments, rather than occlude the aorta, he ligated a large anterior radicular artery near the twelfth thoracic anterior root in 1 monkey and occluded a large anterior radicular artery near the second lumbar anterior root in another monkey. He noted that, in the former case, there was definite degeneration of the dorsal and ventral spinocerebellar and spinothalamic tracts above the lesions and degeneration of the descending fiber tracts below the level of lesion. In the second animal, there was degeneration of all the major ascending and descending fiber systems. Woodward and Freeman[29] ligated 6 adjacent thoracic nerve root pairs with the accompanying blood vessels in a dog and noted the loss of dorsal horn neurons to be constant. They also occluded the aorta for thirty-five minutes, producing irreversible paraplegia. Occlusions of the aorta for less than thirty-five minutes seemed to produce transient changes and often failed to produce any detectable deficit. Eiseman and Summers[30] discussed the factors that affect ischemia of the spinal cord during aortic occlusion and summarized the reports of clinical and experimental cases in the literature, noting the disagreement as to periods of ligation necessary for permanent damage. Adams and van Geertruyden[31] extensively reviewed all clinical reports of aortic occlusion up to 1955 and discussed the mechanism of ischemia of the spinal cord following aortic surgery. They concluded that the minimum safe time of occlusion of the circulation of the spinal cord is still unknown but that it is probably less than eighteen minutes in the human.

The nature of lesions resulting from spinal cord anemia is also a controversial subject. De Buck and de Moor[19] stated that Nissl's stain was the most sensitive and satisfactory for detecting early changes and found they agreed with most workers in that the first change in the nerve cells is chromatolysis and then loss of staining qualities and that the nucleus is

usually more resistant than the cytoplasm to anoxia. Tureen[20] noted a diffuse chromatolysis as the earliest lesion. Marinesco[13,14] alone described swelling of cells as the first change. Jatta[16] and Sabro[11] reported central vacuolization and homogenous atrophy of the nucleus. Swelling, fragmentation, atrophy, and fusion have been described as pathologic changes by various authors. Interstitial reactions, such as capillary dilation, capillary proliferation, and glial proliferation, also have been reported. Gildea and Cobb[32] studied the effect of anemia on the cerebral cortex in the cat and agreed with previous investigators that there is no pathognomic histologic picture of anemia in nervous tissue.

A review of the literature on spinal cord ischemia indicates a difference of opinion regarding the period of ischemia necessary to produce damage, as well as a difference of opinon regarding which areas of the cord are most sensitive to ischemia. Additionally, clinical observations indicate that the syndrome of anterior spinal artery occlusion is much more common than other partial cord ischemic syndromes.

The present study was undertaken to ascertain whether the apparent greater frequency of anterior spinal artery ischemia and the apparent greater sensitivity to ischemia of the anterior part of the cord following aorta ligation might be related to differences in anatomy and physiology of the anterior and posterior spinal artery systems.

MATERIALS AND METHODS

A total of 81 healthy mongrel dogs weighing 7 to 15 kg. and 6 spider monkeys weighing 5 to 8 kg. were used. After intravenous Nembutal anesthesia (25 mg. per kilogram of body weight) and with artificial respiration, the chest was entered through the fourth interspace and the descending aorta immediately distal to the origin of the subclavian artery was ligated for periods of time varying from ten to ninety minutes. Immediately after release of the ligature, 1 mc. of radioactive phosphorus (P^{32}) per 4 kg. of body weight was injected into the femoral vein. The animals were sacrificed two hours after injection, with the exception of a few dogs that were killed one hour after the isotope injection. The spinal cord was removed and fixed in 10% formalin, and sections were taken from each segment of the spinal cord from the upper cervical to the lower lumbar regions; 50-μ. frozen sections and 9-μ. paraffin sections were prepared.

In 4 groups of dogs, the same procedure was followed, with some variations. In group 1, the dogs were injected with Adrenalin, up to 5 cc. (1:1,000) intravenously during the thirty-five minutes' ligation, which maintained a blood pressure in the carotid artery of 30 to 40 mm. Hg above that usually noted. In a second group, the dogs were injected with adenosine triphosphate, up to 500 mg., and histamine, up to 2 mg., intravenously during a twenty-minute ligation to maintain the blood pressure approximately 30 to 50 mm. Hg lower than usual. In group 3, heparin, up to 12 cc. (12,000 units), was injected at the speed of 2 cc. per five minutes during a thirty-five-minute period of ligation. In group 4, up to 250 cc. of blood was withdrawn from the femoral vein during a twenty-minute ligation to prevent the elevation of blood pressure, which was usually caused by clamping the aorta. Immediately after release of the ligature, this blood was returned by way of the femoral vein. In addition, 2 dogs were injected with the usual amount of P^{32} intravenously, and cerebrospinal fluid was then obtained both by cisternal and lumbar puncture (L4-L5) two hours after injection. Radioactivity of the spinal fluid was measured by the usual beta counting technic—Geiger-Mueller tube and planchets. Finally, a similar amount of P^{32} was injected by cisternal puncture in 1 dog and by lumbar puncture (L4-L5) in another dog after aortic ligation for twenty minutes. These dogs were killed two hours after the injections, and sections of the spinal cord were prepared. All 50-μ. sections were exposed to No-Screen x-ray film (Kodak) by contact for four weeks in a refrigerator. The film was developed and studied for evidence of radioactivity. The 9-μ. sections were stained by both cresyl violet and hematotoxylin and eosin and studied microscopically.

RESULTS

In the sections of the spinal cord of animals subjected to occlusion of the aorta for less than twenty-five minutes, with few exceptions, no

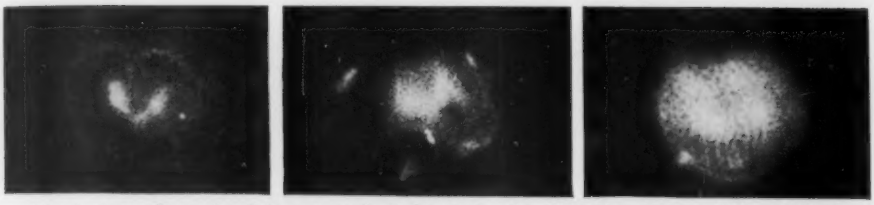

Fig. 1. Autoradiographs of thoracic cord. Radioactivity after thirty-five minutes of ischemia *(left)*, after fifty minutes *(middle)*, and after sixty minutes *(right)*

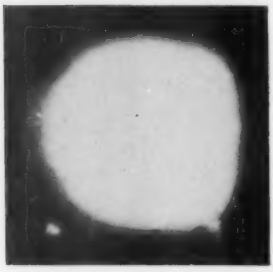

Fig. 2. *(Left)* Autoradiograph of cervical cord two hours after introduction of isotope by cisternal puncture

Fig. 3. *(Right)* Autoradiograph of thoracic cord two hours after introduction of isotope by lumbar puncture

significant radioactivity was recognized. In most specimens, the meningeal membrane was recognized as a very thin dark circle on the negative film (Fig. 1). The results for different periods of aorta ligation are shown in Figures 4 through 12. Radioactivity was most marked with longer periods of ligation.

In general, radioactivity was greatest in the lower cord segments, being less in ascending segments of the thoracic regions. Almost no radioactivity was noted in the lower cervical segments. More radioactivity was found in gray matter, as compared to white matter (Fig. 1, left). No difference was observed between areas supplied by the anterior spinal artery or the posterior spinal arteries. There was no evidence that the region bathed by cerebrospinal fluid had more radioactivity after intravenous injection of P^{32}. In group 1, in which blood pressure was kept higher during ischemia of thirty-five minutes, less radioactivity was detected than expected for that period of ligation and that which was present was in lower segments (Fig. 13). In groups 2 and 4, in which blood pressure was kept lower than usual during ischemia, the cord showed a significant increase in radioactivity (Fig. 14). In the heparinized dogs, there was an apparent slight decrease in radioactivity, as compared to other animals with aortic ligation of thirty-five minutes (Fig. 15). After cisternal injection of radiophosphorus, radioactivity was found in the region around the central canal and the outer border of the cord in all cervical segments and in a few thoracic segments (Fig. 2), while, in the dog injected with P^{32} in the lumbar subarachnoid space, all parts of the cord in every segment showed marked radioactivity (Fig. 3).

The cerebrospinal fluid obtained by cisternal puncture from the dogs injected with P^{32} intravenously revealed 5 times as much radioactivity as that collected by lumbar puncture (L4-L5).

Histologic sections showed minimal and apparently reversible changes in the anterior horn cells in those animals subjected to ischemia for less than thirty-five minutes. After ischemia for forty minutes, more definite changes were noted in neurons and were characterized by swelling and chromatolysis. The anterior horn cells were most frequently involved, but, in those animals subjected to longer periods of ischemia, some of the neurons of the posterior horns also showed these changes.

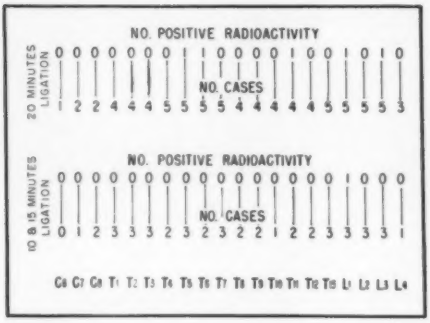

Fig. 4. Frequency of appearance of radioactivity in various segments of spinal cord two hours after aortic ligation of ten to twenty minutes

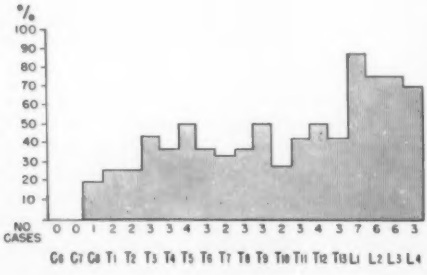

Fig. 5. Distribution of radioactivity in various segments of spinal cord in 8 dogs after twenty-five minutes of aortic ligation

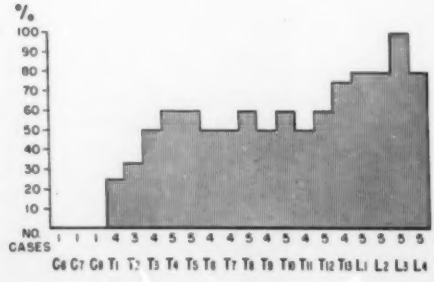

Fig. 6. Distribution of radioactivity in various segments of spinal cord in 5 dogs after thirty minutes of aortic ligation

DISCUSSION

Earlier vital dye experiments have shown that experimental and pathologic injuries to the brain alter the blood-brain barrier within the damaged regions. King [33,34] has demonstrated that all types of lesions are not adequate to alter the blood-brain barrier and expressed the opinion that alteration of the blood-brain barrier to permit passage of trypan blue is dependent upon an inflammatory and necrotizing process. Broman[35] also reported that, as far as experimentation with trypan blue is concerned, the blood-brain barrier is remarkably resistant to the lesions of total anoxia. Nevertheless, recent experiments indicate that a disturbance of the blood-brain barrier may occur without any accompanying edema after simple exposure of the cortex,[36] by injection of certain contrast materials,[37] or by coagulation of the external surface of the intact dura.[38] The amount of radioactive phosphorus which enters the brain tissues from the blood is very small,[39,40] and it has been reported that the uptake of inorganic phosphate into organic combination and the diffusion from plasma into cells are slow.[41] Bakay[42] noted that radioactive phosphorus is deposited in the brain to its entire depth within thirty to sixty minutes after intracisternal injection of P^{32} and ascertained the existence of a blood-brain barrier for P^{32}. He concluded that P^{32} is a more sensitive agent for study of this barrier than a vital dye.[43]

The phosphate ion appears to enter the brain from the blood stream directly through the capillaries in the brain substance or by way of the capillaries of the choroid plexus and cerebrospinal fluid. It has been reported that the amount of P^{32} which enters the brain by way of the blood circulation is very small and, hence, the blood circulation must play a very insignificant role for the uptake of phosphates into the brain.[44,45] Greenberg and associates[46] have determined the velocity by which P^{32} penetrated the cerebrospinal fluid of the dog. An equilibrium was reached between cerebrospinal fluid and blood plasma within two to four hours. There is rapid interchange of phosphate between the cerebrospinal fluid and the brain substance.[42,47] According to Bakay,[48] the highest concentration of the tracer after intravenous injection of P^{32} is to be found in

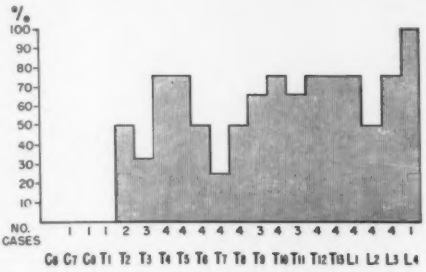

Fig. 7. Distribution of radioactivity in various segments of the spinal cord in 4 dogs after thirty-five minutes of aortic ligation

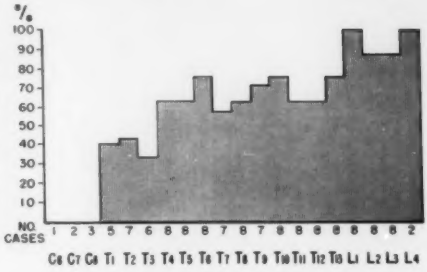

Fig. 8. Distribution of radioactivity in various segments of the spinal cord in 8 dogs after forty minutes of aortic ligation

the internal parts, as well as the surface of the brain, notably in the cortex and ventricular linings. Periventricular areas are highly active during the first hours after injection.

There is no agreement on the role that cerebrospinal fluid plays in the phosphate supply of the brain.[51] Sacks and Culbreth[47] arrived at the conclusion that P^{32} is made available to the brain entirely through the cerebrospinal fluid. Abood and associates[49] challenged this concept by pointing out the importance of phosphate in the utilization of glucose in the brain. It was their opinion that the cerebrospinal fluid pathway is not an essential or important route for the exchange of substances within the central nervous system. Although Dawson[50] concluded that it is impossible to make a definite statement as to the relative importance of the brain capillaries or the spinal fluid as pathways for penetration of substances reaching the brain with the experimental results at present available, Bakay,[48] as the result of his extensive studies on this subject, has concluded the following. During the initial phase of absorption, P^{32} enters the brain by way of the cerebrospinal fluid after it has passed the blood-spinal fluid barrier. This phase is characterized by a large concentration of the tracer within the surface areas and is accompanied by a decline in the radioactivity of the cerebrospinal fluid. The pattern of diffusion is the same whether the tracer has been injected intravenously or intracisternally. The latter phase of absorption reveals a slow and gradual increase of P^{32} concentration in the entire brain, presumably due to a direct passage of the tracer material through the blood-brain barrier. The process of the initial phase remains superimposed on the late phase but becomes less evident as time elapses.

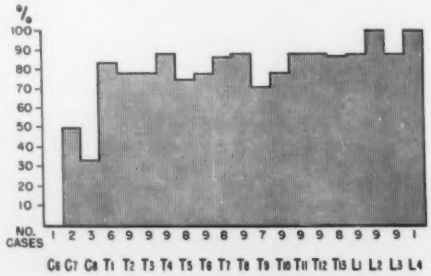

Fig. 9. Distribution of radioactivity in various segments of the spinal cord in 9 dogs after fifty minutes of aortic ligation

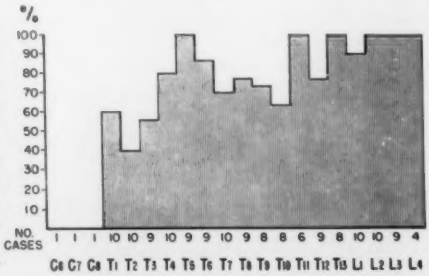

Fig. 10. Distribution of radioactivity in various segments of the spinal cord in 10 dogs after sixty minutes of aortic ligation

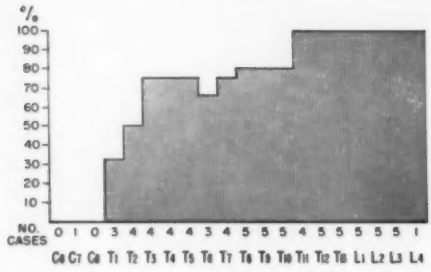

Fig. 11. Distribution of radioactivity in various segments of the spinal cord in 5 dogs seventy and ninety minutes after aortic ligation

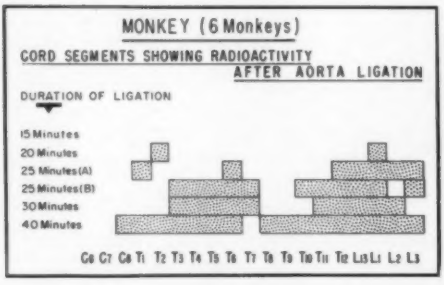
MONKEY (6 Monkeys)
CORD SEGMENTS SHOWING RADIOACTIVITY
AFTER AORTA LIGATION
DURATION OF LIGATION
15 Minutes
20 Minutes
25 Minutes(A)
25 Minutes(B)
30 Minutes
40 Minutes
C6 C7 C8 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 T11 T12 L13 L1 L2 L3

Fig. 12. Distribution of radioactivity in various segments of the spinal cord in monkeys after various periods of aortic ligation

In the present experiments with intravenous injection of P^{32}, there is no evidence that the regions bathed by cerebrospinal fluid had more radioactivity than other parts of the spinal cord. But radioactivity was revealed in the superficial areas and regions around the central canal of all cervical and a few thoracic segments in the dog if the P^{32} was injected intracisternally. When P^{32} was injected in the lumbar subarachnoid space, all parts of the spinal cord were found to be richly radioactive. Furthermore, approximately 5 times as much radioactivity was noted in the cerebrospinal fluid obtained by cisternal puncture, as compared with fluid from the lumbar subarachnoid space two hours after intravenous injection of P^{32}. These data indicate the delay in flow of cerebrospinal fluid from the cisterna magna to the lower spinal subarachnoid space, as compared with diffusion of the P^{32} in the spinal fluid in the opposite direction. This may, in part, be due to the position of the animal, which was slightly head down. Additionally, they indicate that P^{32} penetrates the spinal cord by way of the intramedullary capillaries of the spinal cord rather than by way of the spinal fluid during the first two hours after intravenous injection.

It is generally known that the capillary population of gray matter is 2 to 3 times as great as that of the white matter. In the spinal cord, the ventral gray column has a greater vascularity than do other parts of the cord.[52] However, differences in capillary population do not ap-

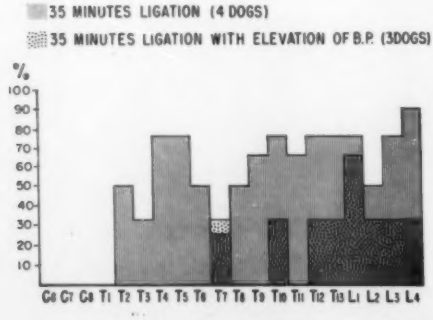

Fig. 13. Effect of blood pressure elevation on distribution of radioactivity in the spinal cord after aortic ligation

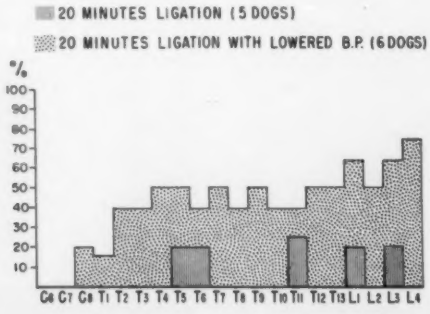

Fig. 14. Effect of lowering blood pressure on the distribution of radioactivity in the spinal cord after aortic ligation

pear to be the sole determining factors as regards P^{32} uptake in the nervous system. Grön-toft[53] studied the P^{32} uptake of various parts of the rabbit brain, using radiogold (Au^{198}) to estimate the relative vascularity at the same time. The amount of P^{32} placed in various parts of the central nervous system was correlated with vascularity as determined by separate counting of Au^{198}. The results indicate that the inequality of the capillary population in various parts of the rabbit brain do not explain the difference in their P^{32} uptake. Abood and associates[54] remarked that the P^{32} turnover in the corpus callosum is higher than in the caudate nucleus, despite the greater blood flow and metabolism of the latter.

It has been suggested that the presence of P^{32} within the capillaries may be misleading in experiments of short duration.[55] However, in the present experiments, although radioactivity was noted in the cord after ischemia lasting more than twenty-five minutes, no significant radioactivity was recognized after ischemia of less than twenty-five minutes' duration. This fact indicates that the existence of P^{32} in the capillaries did not constitute a significant factor in these results. It would appear, then, that the greater concentration of radioactivity in the gray matter, as compared to the white matter, noted in the present experiments was due primarily to ischemia. It is reported that the rate of introduction of P^{32} into brain tissue from blood plasma increases under hypoxia.[55] Whether the existence of P^{32} in the tissue of the spinal cord is due to increasing absorption of nerve cells suffering from ischemia or due to diffusion of P^{32} produced by disturbances of blood–spinal cord barrier is not easy to determine.[56,57] It might be suggested that P^{32} is absorbed by hypoxic nerve cells during an initial phase, then, as ischemia progresses, the blood–spinal cord barrier breaks, causing diffusion of P^{32} from the capillaries into the tissue of cord; later, or superimposed on these processes, the diffusion from cerebrospinal fluid into the tissue might also occur.

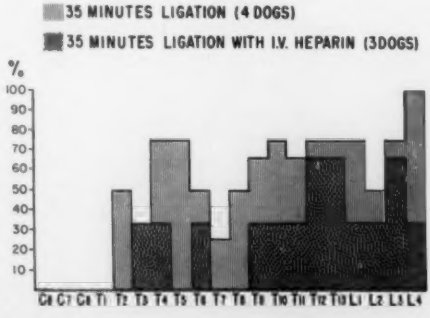

Fig. 15. Effect of heparin on distribution of radioactivity in the spinal cord after aortic ligation

Tureen[29] has reported that ischemic changes were noted in the nerve cells one hour after reestablishment of circulation, after ischemia lasting thirty minutes, but found no histologic changes within seven hours after fifteen minutes' ligation of the thoracic aorta. Neuronal changes did appear after seven hours but were reversible. He concluded that ligation of fifteen minutes' duration is a critical period for production of ischemic changes in the spinal cord. In Hochberg and Hyden's[24] experiments in the rabbit, light spastic paralysis of the hind limbs appeared two hours or more after ligation of the abdominal aorta for fifteen minutes, while ischemia for twenty-five minutes resulted in irreversible changes in the motor cells. The present experiments indicate that twenty-five minutes of ischemia is necessary to produce any significant radioactivity in the cord and thirty-five minutes of ischemia is necessary to produce any significant histologic change. These observations were made two hours after reestablishment of blood flow. It would appear that differing results reported by various workers regarding histologic changes following ischemia may well be related, in part, to the time of examination after the period of ischemia, the animal used, and the method of evaluating the ischemic changes.

The vascular system of the spinal cord has been described by numerous authors.[58–70] In general, 2 arteries arise from the vertebral arteries in the upper cervical portion of the cord or the lower portion of the medulla. These join to form the anterior spinal artery. The anterior spinal artery passes caudally along the midline on the anterior surface of the cord, receiving various contributing branches, the anterior radicular arteries. These arise from the

ascending cervical, deep cervical, intercostal, lumbar, and lateral sacral arteries.[66] The posterior spinal arteries also begin, usually, as branches from the vertebral arteries and continue down the entire cord. These are paired, each posterior spinal artery lying immediately medial to the posterior roots. These form an incomplete arterial chain, receiving various contributions, the posterior radicular arteries.[63,65] The distribution of the radicular vessels is variable and asymmetric. Suh and Alexander[63] found that there are from 6 to 8 anterior radicular arteries and from 5 to 8 posterior radicular arteries. Gillian[70] noted 7 to 10 anterior segmental arteries.

The anterior and posterior spinal arteries are connected by the arteriae coronae, which circle around the outer surface of the spinal cord. The anterior spinal artery contributes the sulcocommissural arteries to supply the deep parts of the cord. After entering the cord, the sulcocommissural arteries arborize in the region of the anterior horn and extend into the adjacent parts of the lateral and posterior column.[71] According to Herren and Alexander,[64] the anterior spinal artery supplies the anterior horn, the central gray matter, the intermediolateral cell column, Clark's column, and the anterior and lateral tracts, including anterior and lateral pyramidal tracts. According to Bolton,[67] this artery supplies most of the gray matter and the anterior portion of the posterior white column. The posterior spinal arteries supply the posterior portion of the posterior gray column and the major portion of the posterior white column.[64,67] The venous system of the spinal cord follows a pattern similar to that of the arterial system except for a greater variability in number and distribution of radicular veins and the presence of 1 longitudinal venous channel on the posterior surface of the cord.

In general, the anterior and posterior spinal veins drain the anterior one-half to two-thirds and the posterior one-third to one-half of the spinal cord.[65,66] This general vascular pattern is true of all mammals with few exceptions. In the monkey[65] and the cat,[68] the radicular arteries are more numerous and more symmetric, and, in the cat, there is an extensive anastomosis between anterior and posterior spinal arteries within the dorsal horn which has not been described in man.[68] In the rat, the arterial supply of the cord is similar to that of man.[69]

In the present experiments, ligation of the aorta immediately below the origin of the subclavian artery eliminates the contributions to the spinal cord circulation of all radicular arteries below the cervical region. Thus, the capabilities of circulation along the posterior and anterior spinal arterial system below the cervical region can be studied.

In the present experiments, after aorta ligation, no difference in radioactivity was noted between the area supplied by the anterior spinal artery and that supplied by the posterior spinal arteries. In addition, these areas were equally affected in the experiments in which the blood pressure was elevated or lowered during the period of ligation and in those experiments in which heparin was administered during the period of ischemia. These data suggest that either both systems have approximately equal capabilities of acting as collateral pathways for circulation or that there is free interchange between the 2 systems throughout their length below the first thoracic segments. The clinical observations that anterior spinal artery thrombosis is more frequent than posterior spinal artery occlusion are probably not the result of greater capabilities of the posterior spinal artery system to act as collateral pathways, due to basic anatomic or physiologic characteristics in the absence of vascular disease, but rather to some other reason not apparent in this study.

In the present experiments, after aorta ligation, no increased radioactivity was noted in the cervical cord segments. These data suggest that the border between the areas supplied by the subclavian artery and that supplied by the aorta is in the region of the lower cervical or upper thoracic cord. This is in agreement with observations made by others using injection technics and clinicopathologic observations.[67,74,75] This observation also tends to explain the greater frequency of spinal artery occlusion syndromes in this region.

The concept that the more peripheral areas of a vascular system are more vulnerable to ischemia has been well established.[72–75] The present observations that, after aorta ligation, there were increasing amounts of radioactivity appearing in the cord in descending segments

expresses this concept, the lowest segments of the cord being the most vulnerable to ischemia and the ascending segments showing less vulnerability under these circumstances.

SUMMARY

Difference in extent and degree of penetration of tracer amounts of radiophosphorus (P^{32}) in the spinal cord in dogs and monkeys following ischemia for various periods of time were studied by autoradiography. Ischemia was produced by temporary occlusion of the descending aorta immediately distal to the origin of the subclavian artery. Ischemia of twenty-five minutes or longer allowed the P^{32} to pass the blood–spinal cord barrier, but less than twenty-five minutes did not alter the barrier sufficiently to allow significant penetration of P^{32}. Radioactivity was most marked with longer periods of ischemia and was greatest in the lower segments, being less in ascending segments of the thoracic region. No increase in radioactivity was noted in the lower cervical segments. Although more radioactivity was found in gray matter as compared with white matter, no differences were observed between the areas supplied by the anterior or posterior spinal arteries. The significance of these data in relation to spinal cord circulation and blood–spinal cord barrier were discussed.

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Effect of D,L-penicillamine on the urinary excretion of copper and calcium in hepatolenticular degeneration (Wilson's disease)

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Excessive accumulation of copper in certain organs such as the liver, brain, and kidneys has been postulated as responsible for the symptomatology in patients with hepatolenticular degeneration. Consequently, in the treatment of this disease, substances have come into use which decrease the absorption of copper from the gastrointestinal tract or promote the excretion of copper from the body. In general, these substances can be divided into 3 groups on the basis of their presumed action as follows: [1] to decrease the absorption of copper from the gut, [2] to increase the urinary excretion of copper, and [3] to increase the concentration of plasma ceruloplasmin. Treatment to decrease the absorption of copper from the gut includes a low copper diet and administration of potassium sulfide or ion exchange resins. Therapy that will increase the excretion of copper in the urine includes intravenous administration of Calcium Disodium Versenate, intramuscular injection of British antilewisite (BAL), high protein diet, intravenous use of amino acids, and the administration of cortisone.

It has been postulated that the low plasma ceruloplasmin is the stimulus for increased absorption of copper from the gastrointestinal tract and its deposition in tissues. Estrogens and the intravenous administration of ceruloplasmin have been used in an attempt to increase the concentration of plasma ceruloplasmin.

Of all these substances, BAL has been the one used as standard treatment for hepatolenticular degeneration. However, it has several disadvantages, one of them being that it must be given intramuscularly, which may prove painful after prolonged administration. Also, it may cause undesirable side effects and may not result in improvement of the patient's condition.

Walshe[1] in 1956 and Fister, Boulding, and Baker[2] in 1958 reported on the use of penicillamine, a degradation product of penicillin, in the treatment of hepatolenticular degeneration. The advantages of penicillamine lie in its stability, oral use, and rapid excretion by the kidneys. Also, the urinary excretion of copper during administration of penicillamine is far greater than with BAL.

In a previous communication,[3] we reported the finding of hypercalciuria in 4 of 5 patients with hepatolenticular degeneration. In an attempt to learn about the effect of D,L-penicillamine on the urinary excretion of calcium and copper, further studies were carried out in these same 5 patients. The urinary excretion of calcium and copper, as well as other urinary constituents, was studied before and during the administration of D,L-penicillamine.

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TABLE 1
EFFECT OF D,L-PENICILLAMINE ON URINARY EXCRETION OF COPPER AND CALCIUM IN HEALTHY PERSONS

	Copper		Calcium	
Healthy person	*Control, mg. per 24 hr.*	*D,L-Penicillamine,* mg. per 24 hr.*	*Control, mg. per 24 hr.*	*D,L-Penicillamine,* mg. per 24 hr.*
	0.14	1.71	47	28
	0.12	1.72	50	43
	0.12	1.54	39	36
A	Average 0.13	Average 1.66	Average 45	Average 36
	0.11	1.63	147	134
	0.08	1.80	172	185
	0.08	1.62	164	177
B	Average 0.09	Average 1.68	Average 161	Average 165
	0.04	1.33	61	69
	0.03	1.49	56	66
	0.05	1.41	92	65
C	Average 0.04	Average 1.41	Average 70	Average 67

*Dose: 500 mg. of D,L-penicillamine orally three times a day

The patients had not received any treatment for one to four months before the study. In addition, similar studies were carried out on 3 healthy men.

METHOD

The weighed diet used in this study contained 2,223 calories consisting of 62 gm. of protein, 111 gm. of fat, and 244 gm. of carbohydrate per twenty-four hours. Distilled water as desired was used as drinking water. The daily intake of calcium and copper was estimated to be 213 mg. and 2.93 mg., respectively, as determined by chemical analysis of an aliquot of a twenty-four-hour diet plus 1,900 cc. of distilled water.

With each person, the diet was started with an evening meal and then continued for the next three days, which constituted the control period. During this period, 3 specimens of urine, each collected over a twenty-four-hour period, were analyzed for *p*H and content of calcium, copper, ammonia nitrogen, titratable acidity, total nitrogen, alpha-amino nitrogen, and phosphorus. The same studies were then done over a second three-day period, during which each person was given 500 mg. of D,L-penicillamine orally half an hour before each meal, a total of 1,500 mg. per twenty-four hours. In each instance, the diet and administration of D,L-penicillamine were begun the evening immediately preceding the three-day period of study.

The diet, collection of urine, and some of the chemical methods have been described in detail in our previous paper.[3] In addition, the following methods were used for the determination of urinary constituents: phosphorus, by a modification of the Gomori method;[4] alpha-amino nitrogen, by a modification of the method of Pope and Stevens;[5] titratable acidity, by the method of Henderson and Palmer;[6] ammonia, by aeration and titration;[7] and total nitrogen, by the Kjeldahl method. Some of the data obtained during the control period as well as an abstract of each patient's history have also been presented in our previous paper.[3]

RESULTS AND COMMENT

The effect of D,L-penicillamine on the urinary excretion of copper and calcium in the 3 healthy men is shown in Table 1. The urinary excretion of copper increased 13 to 35 times in these 3 persons while they received D,L-penicillamine as compared with the control period. However, D,L-penicillamine did not produce a significant change in the urinary excretion of calcium (Table 1).

In the 5 patients with hepatolenticular degeneration, D,L-penicillamine increased the urinary excretion of copper 4 to 17 times (Table 2). As with our healthy persons, D,L-penicillamine did not appear to have a consistent effect on the urinary excretion of calcium in our 5 patients. Though the average figures might suggest some changes, a comparison of the excretion of calcium in the

TABLE 2

EFFECT OF D,L-PENICILLAMINE ON URINARY EXCRETION OF COPPER AND CALCIUM IN 5 PATIENTS HAVING HEPATOLENTICULAR DEGENERATION

Case	Copper		Calcium	
	Control, mg. per 24 hr.	D,L-Penicillamine,* mg. per 24 hr.	Control, mg. per 24 hr.	D,L-Penicillamine,* mg. per 24 hr.
	1.01	3.83	192	187
	1.04	4.53	207	182
	1.07	4.36	200	196
1	Average 1.04	Average 4.24	Average 200	Average 188
	1.12	7.85	233	271
	1.06	10.70	239	285
	0.81	9.25	246	267
2	Average 1.00	Average 9.27	Average 239	Average 278
	0.70	10.15	350	376
	0.60	9.00	404	478
	0.42	10.35	332	340
3	Average 0.57	Average 9.83	Average 362	Average 398
	0.26	2.99	126	198
	0.33	3.67	116	188
	0.24	4.60	125	193
4	Average 0.28	Average 3.75	Average 122	Average 193
	0.46	5.76	362	238
	0.37	5.53	210	305
	0.44	3.99	292	214
5	Average 0.42	Average 5.09	Average 288	Average 252

*Dose: 500 mg. of D,L-penicillamine orally three times a day

TABLE 3

EFFECT OF D,L-PENICILLAMINE* ON URINARY CONSTITUENTS IN 3 HEALTHY PERSONS AND 5 PATIENTS WITH HEPATOLENTICULAR DEGENERATION†

		Volume, cc. per 24 hr.	pH	Ammonia, nitrogen mEq. per 24 hr.	Titratable acidity, mEq. per 24 hr.	Total nitrogen, mg. per 24 hr.	Alpha-amino nitrogen, mg. per 24 hr.	Phosphorus, mg. per 24 hr.
Healthy person								
	Control	1820	6.4	37.3	24.0	12,435	282	748
A	DLP	1472	6.5	35.1	27.7	12,821	398	792
	Control	1630	6.6	33.1	16.2	12,299	405	915
B	DLP	1352	6.8	34.4	13.8	11,666	434	809
	Control	735	5.9	27.7	25.1	10,892	288	723
C	DLP	1393	6.6	27.2	16.6	11,162	377	686
Case								
	Control	2270	6.6	25.2	15.0	11,154	924	767
1	DLP	2850	6.6	27.3	18.3	10,600	962	734
	Control	1647	—	—	—	12,190	570	—
2	DLP	1963	—	—	—	11,390	771	—
	Control	1243	—	—	—	7,820	509	—
3	DLP	1147	—	—	—	9,050	775	—
	Control	1408	6.7	50.0	7.6	9,617	458	571
4	DLP	1610	6.5	39.0	8.9	10,167	554	652
	Control	910	6.4	30.8	16.1	5,850	669	510
5	DLP	2010	6.9	24.6	14.5	6,267	642	450

*Dose: 500 mg. of D,L-penicillamine orally three times a day
†Each value is the mean of 3 twenty-four-hour periods.

urine for each day reveals much overlapping and no significant change. The only exception might be in Case 4.

Table 3 shows that the administration of D,L-penicillamine did not cause significant change in urinary *p*H, titratable acidity, ammonia production, alpha-amino nitrogen, total nitrogen, or phosphorus as compared with the values during the control period in either the healthy men or the patients with hepatolenticular degeneration in whom these studies were done.

Our findings are in accord with those of Walshe[1] on the effect of penicillamine on urinary excretion of copper by patients with hepatolenticular degeneration as well as by normal persons. In addition, Walshe demonstrated in a short-term study that penicillamine was superior to BAL in promoting the urinary excretion of copper. Our experience agrees with this. Of our patients, 2 (Cases 2 and 3) received BAL intramuscularly (2.5 mg. per kilogram of body weight) twice daily for three to five days. Each showed a twofold increase of urinary excretion of copper while receiving BAL. This is in contrast with the ninefold to seventeenfold increase in excretion of copper in the same patients while they received D,L-penicillamine.

Since D,L-penicillamine binds copper so readily, it is logical to ask if the increased urinary excretion of copper is not simply the result of increased absorption of copper from the gastrointestinal tract; 2 findings mitigate against this possibility being the sole explanation. In the first place, Walshe[1] noted a significant increase in the urinary excretion of copper with the intravenous administration of penicillamine in a patient with hepatolenticular degeneration. Second, as is shown in Table 2, the urinary excretion of copper by all of our patients while receiving D,L-penicillamine was greater than the total of the control excretion plus the daily copper content of the diet. This suggests that D,L-penicillamine is effective in mobilizing copper from the tissues.

SUMMARY

The oral administration of D,L-penicillamine greatly increases the urinary excretion of copper in patients with hepatolenticular degeneration and in healthy subjects. It far surpasses the effect of BAL in this regard and has the advantage of oral administration. The data suggest that the increased urinary excretion of copper represents actual mobilization of copper from tissues. D,L-penicillamine has no significant effect on the urinary excretion of calcium or phosphate. Likewise, it does not produce significant change in the urinary *p*H, titratable acidity, total nitrogen, ammonia nitrogen, or alpha-amino nitrogen.

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Optokinetic nystagmus in cerebral disease

A report of 14 autopsied cases

J. Lawton Smith, M.D., and David G. Cogan, M.D.

OPTOKINETIC NYSTAGMUS is an involuntary oscillation of the eyes induced by viewing a succession of moving objects. It is symmetric, or nearly so, to either side in the normal individual, and such a response has been defined as a "*negative* O.N. sign."[1] A defective response to one side in the presence of an intact response to the other side on rotating targets is a "*positive* O.N. sign." The latter, or asymmetric, optokinetic response has been stressed as a useful, easily elicited localizing neurologic sign.[2–5]

Cords[6] considered an asymetric response as indicative of an efferent optomotor lesion, with the most likely site in the internal and external sagittal strata of the middle and posterior one-third of the optic radiations. Kestenbaum[1] analyzed a series of 59 cases of homonymous hemianopia, in which the lesions had been localized by autopsy, surgery, or roentgenogram. The number of cases in each of these 3 subdivisions was not stipulated. He considered a negative O.N. sign as 100% reliable in excluding a parietal lobe origin for a homonymous hemianopia. Opinions of the value of a positive O.N. sign have varied,[1–7] but most authors have considered it as indicative of disease involving the posterior half of the cerebrum. The rare instances of alleged frontal lobe disease causing an asymmetric optokinetic response have not excluded parietal lobe involvement.[5,7] It is evident that more information is needed on anatomically verified cases to resolve the significance of a positive optokinetic nystagmus sign.

Our clinical experience has borne out the impressions of Cords and Kestenbaum that this simple test is a reliable sign of parietal lobe localization in cerebral disease and that one can, with reasonable assurance, differentiate temporal and occipital lobe hemianopias from those of parietal origin by this method. The purpose of this report is to present the clinical and pathologic findings in 14 patients in whom the optokinetic response has been carefully studied and who have subsequently come to autopsy examination. A review including cases studied histologically from surgical biopsy material is the subject of another paper.[8]

MATERIAL

A total of 194 cases of cerebral disease seen by Dr. Cogan has been reviewed. The cases selected had been referred because of suspicion or presence of a homonymous hemianopia. Of these 194 cases, 29 have come to necropsy in the Massachusetts General Hospital. In 14 of the latter, a specific statement regarding optokinetic nystagmus is available. These were selected for further analysis.

CASE REPORTS

Case 1. A-15772. *Clinical summary.* This 32-year-old white female was first admitted to the Massachusetts General Hospital because of uncinate seizures of ten months' duration. The only complaint referable to the eyes was inability to remember material she had recently read. Neurologic examination revealed only a slight right facial weakness. Ophthalmologic examination revealed normal visual fields and 20/20 vision in both eyes. A normal optokinetic response was noted. The following day, a left posterior temporal lobe

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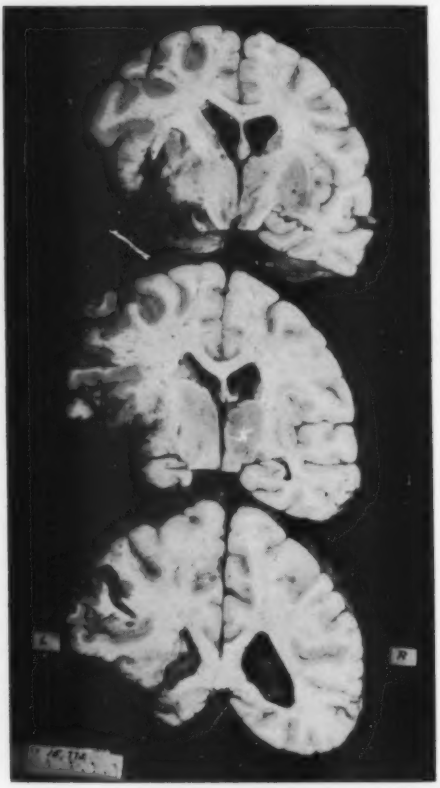

Fig. 1. Case 1

astrocyotma was resected. On the fifth postoperative day, a complete right homonymous hemianopia was noted to confrontation. She did well for forty-one months but was then readmitted with recurrent headaches. Neurologic examination then revealed only a lower right facial weakness and slight right hyperreflexia. Eye examination revealed 20/30 vision in the right eye and 20/40 in the left eye, with temporal pallor of the right disk. There was a complete right homonymous hemianopia splitting fixation. A positive optokinetic nystagmus sign was now present. Forty-seven months after the first operation, a repeat left parietooccipital craniotomy was performed. The neoplasm was found to have recurred and extended into the frontal, parietal, and occipital lobes on the left, as well as into basal ganglia and posterior fossa. The patient died twelve hours later.

Pathologic summary (Fig. 1). At necropsy, on gross examination there appeared to be a glioma in the left parietotemporal region and the left hemisphere seemed infarcted. The brain weighed 1,330 gm. A large operative defect was seen, with virtually the entire left temporal lobe being absent. On coronal sections, gross neoplasm was seen lateral, inferior, and anterior to the anterior horn of the left lateral ventricle. The tumor involved the left lenticular nucleus anteriorly and also the lateral portion of the left thalamus. The anterior and posterior limbs of the left internal capsule were also involved. The left uncus was herniated. The left cerebrum was swollen. No abnormality was seen in the right hemisphere. The vessels at the base were normal. On section, the midbrain showed left-sided swelling, with aqueductal shift and distortion to the right. The cerebellum and remainder of the brain stem were normal. Anatomic diagnoses were glioblastoma multiforme, left temporofrontal, and herniation, left uncus, causing compression and 2 midbrain hemorrhages.

Comment. This 32-year-old woman had a glioma of the left temporal lobe. One day preoperatively, her vision, fields, and optokinetic responses were normal. On the fifth postoperative day, a complete right hemianopia was noted. Forty-one months later, with a recurrence of the tumor, a positive O.N. sign was seen. Autopsy revealed a glioblastoma multiforme with definite involvement in the left parietal lobe. No neoplasm was found in the right cerebral hemisphere. This case is important in showing no abnormality of optokinetic nystagmus as long as there was only temporal lobe involvement. A positive optokinetic nystagmus sign was noted only later, when definite parietal extension was seen.

Case 2. A-14525. *Clinical summary.* This 70-year-old white female was admitted with a five-month history of episodes of semistupor and inability to talk, associated with smacking movements of the lips. She had been hypertensive for ten years. A doctor had noted that she was confused and that she could form words and speak but could not identify objects verbally. Progression of the dysphasia, along with weakness in the right upper extremity, prompted hospitalization.

Neurologic examination revealed motor aphasia, right-sided hyperreflexia, weak grip on the right, increased rigidity and poor coordination in the right extremities, equivocal Babinski responses, and absent position, vibratory, pinprick, and light and deep touch responses on the right.

Ophthalmologic examination revealed visual acuity of 10/30 in both eyes, but testing was difficult due to the aphasia. The fundi were normal. A complete right homonymous hemianopia was present. A positive optokinetic nystagmus sign was noted, with no response on rotating the drum to her left but an intact response on rotating tar-

gets to her right. Lack of recognition of the right arm was noted, making the case essentially a Gerstmann's syndrome. The differential diagnosis lay between thrombosis of the left middle cerebral artery and an extensive infiltrating tumor of the left parietal lobe.

At the family's request, a left parietooccipitotemporal craniotomy was performed and revealed a necrotic glioma. The patient died one week later.

Pathologic summary (Fig. 2). The left hemisphere was larger than the right. The convolutions were flattened, more so on the left. But for scattered atheromatous plaques, the vessels at the base were normal. Bilateral cerebellar pressure cones were present.

On coronal sections, herniation of the left cingulate gyrus beneath the falx was seen. The left lateral ventricle was distorted and displaced. In a section at the level of the left thalamus was a tumor with ill-defined edges involving the left thalamus, basal ganglia, and roof of the lateral ventricle. This tumor extended posteriorly to the occipital lobe, involving almost the entire lobe except for a small area 1 cm. from the dorsal border. No gross evidence of tumor in the temporal lobe was noted, except in the roof of the temporal horn of the lateral ventricle.

At the level of the splenium, the tumor was friable with larger areas of hemorrhage and necrosis than in its anterior portions. The midbrain was distorted with the left side compressed. The sylvian aqueduct was a vertical slit due to compression. The pons was slightly flattened from left to right. The medulla and cerebellum were unremarkable. Anatomic diagnosis was glioblastoma multiforme.

Comment. Right homonymous hemianopia, right hemianesthesia, and increasingly severe symptoms pointing to the same locality in the brain were correlated with an infiltrating tumor in the left thalamic and parietooccipital regions in this patient. This is an instance of a parietal lobe tumor that was associated with a positive optokinetic nystagmus sign.

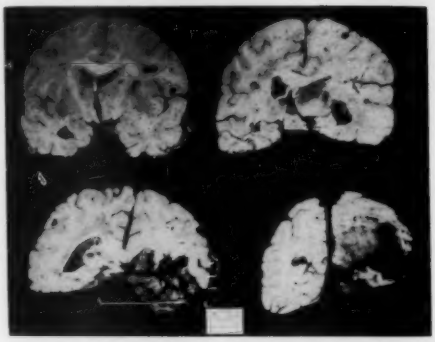

Fig. 2. Case 2

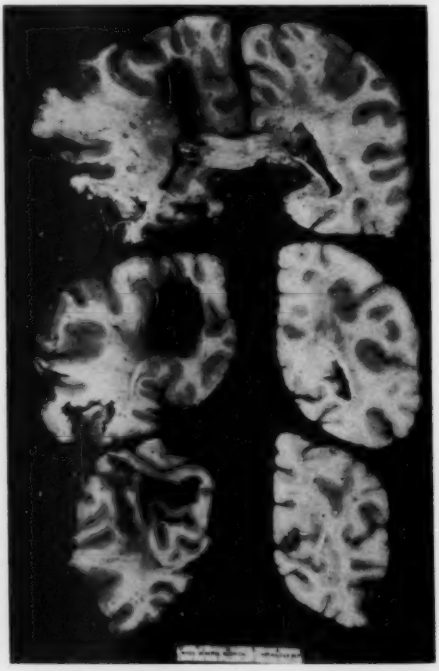

Fig. 3. Case 3

Case 3. A-16545. *Clinical summary.* This 59-year-old white woman was well until fourteen months before admission, when she began to fall asleep in midmorning for three to four hours, shortly after a good night's sleep. One year before admission, headaches and fatigability began. She became unsteady on her feet and had tinnitus and hearing loss on the left four months before admission.

Neurologic examination revealed a tendency to fall to the right when she stood with eyes closed; certain alternating movements were less well performed with the right hand, and a right lower facial weakness was apparent on emotional stimuli. On the third hospital day, a right carotid arteriogram disclosed a mass lesion in the anterior right temporal lobe, which appeared relatively avascular. The next day, ophthalmologic examination revealed 20/40 vision in both eyes, sluggish and unequal pupils with the left slightly smaller, and a fine horizontal nystagmus on left lateral gaze. The fundi were normal. A homonymous left upper quadrantanopia was present to 10/1,000 white and

was also absolute to hand movements at 1 meter. The optokinetic response was brisk and equal to each side. On the fifth day, craniotomy disclosed a meningioma in the right sylvian fissure. The tumor was encountered growing from the dura into the sylvian fissure; at surgery, it was possible to lift the entire tumor out of its bed and remove it in 1 specimen. However, postoperatively, the patient had dilated fixed pupils, was comatose, and was taken back to the operating room six hours later. Marked bulging of the brain through the bur holes occurred, so that many small venous channels on the surface tore. Despite a massive decompression, the patient died on the following day.

Pathologic summary (Fig. 3). The surgical specimen was histologically a meningioma. Necropsy disclosed marked cerebral edema, predominantly of the right hemisphere, with a right temporal pressure cone. A fresh hemorrhage was noted in the right parietooccipital region. The cerebellum and brain stem were normal.

Comment. This patient died of uncontrollable cerebral edema and hemorrhage after a craniotomy at which a meningioma of the right anterior temporal region had been completely excised. A left upper homonymous quadrantanopia and intact optokinetic nystagmus were present preoperatively. The fresh hemorrhage noted at autopsy was undoubtedly secondary to surgery, since no parietal lobe involvement was seen at craniotomy and the neoplasm had been apparently removed intact. This case clearly demonstrates a focal lesion of the temporal lobe producing a Meyer's loop field defect and a negative optokinetic nystagmus sign.

Case 4. A-20647. *Clinical summary.* This 76-year-old physician presented a complex and involved history. He had old bilateral apical scars from a healed tuberculosis. Twenty-one months before death, the shadow on the right began to enlarge. Nine months before death, he suddenly noted a visual field defect. Examination revealed vision of 20/70 on the right and 20/30 on the left. Incipient lens changes were considered adequate to account for the vision. Optokinetic responses were symmetric to both sides. A right homonymous paracentral scotoma was found, most dense near the center, with sharp splitting of the point of fixation. Ophthalmodynamometry disclosed equal ophthalmic artery diastolic pressures. No deviation of the eyes was seen on forced lid closure, and the fundi were not remarkable. The patient was placed on anticoagulant therapy. He later developed an abdominal mass, signs of diffuse metastatic disease, and a right third nerve palsy and died eight months later.

Pathologic summary. The brain weighed 1,245 gm. Vessels at the base revealed moderate atherosclerosis but no significant narrowing. A small focal scar was seen on the external surface of the right frontal lobe, which on section was a small cystic infarct. The surface of the left occipital lobe revealed yellowish-gray tumor covering the arachnoid and adherent to the underlying brain. Tumor was seen in the meninges on the medial aspect of the right occipital lobe but did not appear to involve underlying brain. In several areas, tiny 2- to 3-mm. foci of softening were seen in the cortex and adjacent white matter. The left occipital lobe on section revealed extensive, partly necrotic tumor, extending 1.5 to 2.5 cm. down from the surface and replacing all of the visual cortex.

Sections of the cerebellum revealed the superior three-fourths of the left hemisphere replaced by tumor that extended across the midline to involve the medial one-third of the right hemisphere. Tumor was also noted on dural surfaces of falx, tentorium, and venous sinuses. The right intracranial portion of the third nerve was normal. However, in the superior orbital fissure, it was surrounded by gray-white firm tumor tissue. The surrounding bone was grossly uninvolved. Metastatic tumor was seen in the cauda equina, but the remainder of the spinal cord was negative. Anatomic diagnoses included adenocarcinoma of lung, right upper lobe bronchus, with metastases to liver, right adrenal, and right kidney; metastatic tumor to occipital lobes, dura, right third nerve, and cauda equina; cerebral atherosclerosis with multiple small infarcts, most prominent in right frontal lobe; and pulmonary tuberculosis, apical, bilateral, healed.

Comment. This patient presented a diagnostic problem. When a right homonymous hemianopia appeared, differential diagnosis lay between metastatic tumor and vascular disease. As transient blindness in the right eye had been noted previously, cerebral vascular disease was considered likely and he was treated with anticoagulants. It should be noted that ophthalmodynamometry had disclosed equal diastolic pressures in the 2 eyes. Later, metastatic disease and a terminal right third nerve palsy were apparent. The point to be stressed here is that, with definite metastatic disease confined to the occipital lobes, producing a right homonymous paracentral scotoma, a negative optokinetic nystagmus sign was found. There was no parietal lobe involvement in this case.

Case 5. A-18902. *Clinical summary.* This 59-year-old white male was hospitalized because of drifting to the left side, dizziness, and headache for one week. In retrospect, his wife had noted

a gradual increase in forgetfulness during the preceding six to eight months. Seven days before admission, he began to drift to the left and even to bump into objects on his left and would stumble or fall in doing this. Five days before admission, he became less aware of the left side of his environment in general. The only other symptoms were headache and fatigability.

Neurologic examination revealed that, although he was oriented, there was some evidence of intellectual deterioration. A questionable left facial weakness, poorly performed finger-to-nose test and alternating movements on the left, falling to the left on Romberg testing, and a left Babinski response were noted.

Ophthalmologic examination revealed normal vision, fields, and fundi and no defects, except in optokinetic nystagmus. A positive O.N. sign was found, with a definitely poorer response on rotating the drum to his right than to his left. Electroencephalograms and radioactive arsenic pointed to a right postfrontal lesion. A right carotid arteriogram demonstrated that the ascending frontoparietal branch of the middle cerebral was straightened and lacked its usual tortuous character.

A right temporal craniotomy was performed, with subtotal resection of a subcortical right frontal tumor just rostral to the premotor strip. The patient did not respond postoperatively and died the following day.

Pathologic summary. A large surgical defect in the right frontal area, a right temporal pressure cone, and herniation of the falx were seen. Vessels at the base were normal. On section, the right hemisphere was the larger, and the ventricular system was shifted to the left. Deep in the right frontoparietal region was a large hemorrhagic defect with only a few areas of necrotic tumor tissue remaining. The largest diameter measured 4 x 1¾ cm. Surrounding this, the white matter was soft and discolored. A circumscribed tumor nodule 1 x 1 cm. was found in the left island of Reil. In the right basal ganglia was a small linear hemorrhage. The brain stem and cerebellum were normal.

Microscopic examination revealed a grade 3 to 4 astrocytoma in the right frontoparietal region. The tumor nodule in the left insula revealed minimal tendency to infiltrate surrounding brain tissue. Brain tissue adjacent to the tumor masses was grossly edematous. A recent infarct necrosis was seen in the midbrain. Anatomic diagnoses included glioblastoma multiforme (astrocytoma grade 3–4), right frontal lobe, infiltrating and left frontal lobe, circumscribed, and cerebral edema.

Comment. This 59-year-old man presented a one-week history of ignoring the left side of his environment and had a pseudohemianopia to the left. The only abnormality on eye examination was a positive optokinetic nystagmus sign. The clinical evidence pointed to a right frontal lobe neoplasm. However, the optokinetic asymmetry correlated with definite neoplastic involvement found in the right parietal lobe at autopsy.

Case 6. A-15154. *Clinical summary.* This 44-year-old left-handed white male was admitted with a three-year history of infrequent generalized clonic seizures, dizziness, increased sleepiness and lethargy, and progressive stiffness and tremor in the right upper extremity.

Examination revealed cog-wheel rigidity and hyperreflexia in the right upper extremity. There was a pseudohemianopia to the right. Skull roentgenograms revealed left frontotemporal calcification. An air study revealed displacement of the ventricular system to the right. No abnormalities were noted on eye examination. The fields were full, and the optokinetic responses were symmetric. The following day, a left frontal lobectomy was performed for glioma, but the patient died on the third day.

Pathologic summary. The left hemisphere was enlarged, and the left cingulate gyrus was herniated beneath the falx. Convolutions were flattened over both hemispheres. A right cerebellar pressure cone was present. The left occipital lobe was softened. On section, the operative defect began near the left frontal pole, was 5 cm. deep, and was filled with blood and fibrin foam. In the remaining white matter of the frontal cortex, the left basal ganglia, and the genu and body of the corpus callosum, the brain tissue was yellowish and softer than surrounding brain. The left occipital pole, left peduncle, and midbrain were softened. A hemorrhage was seen in the center of the pons, and the midline structures were shifted to the right. Anatomic diagnoses included mixed glioma, left frontal lobe, and pulmonary edema.

Comment. A mixed glioma of the left frontal lobe produced symptoms for three years. Although there was a right pseudohemianopia, the visual fields were normal. At autopsy, the basal ganglia and anterior internal capsule were involved on the left but extension into the parietal lobes was lacking. This was an example of a frontal lobe tumor with no parietal lobe involvement and negative optokinetic nystagmus sign.

Case 7. A-13413. *Clinical summary.* This 45-year-old white female had had generalized grand mal seizures for ten years. These began in the left side of the face and were associated with turning of the eyes to the left, loss of responsiveness, tongue biting, frothing at the mouth, respiratory difficulty, and urinary incontinence. For two years, a gradual personality change had occurred, and she became listless and confused, with a definite

Fig. 4. Case 7

memory impairment. Whereas formerly quite emotional, she could no longer cry. She had urinary incontinence for six months and headaches for one month.

Examination revealed a left peripheral facial weakness, slight weakness of the left upper extremity, slowness of speech with some lack of comprehension, slight tremor and questionable dysdiadochokinesis of the left upper extremity, Babinski response on the right, right-sided anosmia, and incontinence.

Ophthalmologic examination revealed bilateral papilledema, sluggish pupils, and an incongruous left homonymous hemianopia, but the patient was too drowsy to give consistent answers. A definite defect was noted in the optokinetic response with targets to the right.

At right frontotemporal craniotomy, a dense, firm glioma was encountered astride the sylvian fissure. A partial excision of the tumor was performed. The postoperative course was stormy, with a meningitis, and the patient died seventeen days later.

Pathologic summary. The dura over the posterior half of the right frontal lobe was yellowish-brown and adherent to the underlying cortex. Bilateral cerebellar and temporal pressure cones were present. The basal arteries had slight atherosclerosis. On section, the cortex and subcortical white matter of the right superior and middle frontal convolutions were soft and necrotic. The deeper white matter was slightly soft and contained several hemorrhagic areas. Further posteriorly, the right thalamus, internal capsule, basal ganglia, and part of the white matter of the parietal and temporal lobes were smooth and firm to palpation. A small cavity was seen in the right thalamus. The anterior horn of the right lateral ventricle was partially collapsed, but the remaining portion and left lateral ventricle were dilated to 4 times normal size. The brain stem and cerebellum were not unusual. Histologically, an astrocytoma was seen. In some regions, infiltration of the cortex by neoplastic cells with preservation of cortical architecture and many of the nerve cells had occurred (Fig. 4).

Comment. One could have considered this, on gross examination, to have been a frontal lobe tumor with a positive optokinetic nystagmus sign. However, on section, there was tumor in the right parietal lobe, and microscopic examination revealed a diffusely infiltrative astrocytoma.

Case 8. A-12292. *Clinical summary.* This 38-year-old white male was first admitted for secondary syphilis and was treated with penicillin. Five months later, a routine lumbar puncture was negative. Three months after that, he noted increasing headaches with episodes of hallucinations, dizziness, and occasional burning sensations of the nose, with feeling of obstruction and peculiar odors. Three days before his second admission, lumbar puncture revealed 118 cells, protein 150 mg. per cent, and he was readmitted for suspected meningovascular syphilis.

The blood and spinal fluid serologic tests for syphilis were negative. Neurologic examination revealed a left hemiparesis and defective smell on the right. Eye examination revealed 20/40 vision on the right and 20/50 on the left. A complete left homonymous hemianopia splitting fixation was found. The fundi were normal. A positive optokinetic nystagmus sign was present, with an absent response on rotating the drum to his right. Encephalographic examination revealed a shift of the ventricular system to the left, consistent with a deep and large right temporal tumor. At craniotomy, subtotal removal of an invasive glioma was performed. The patient died on the third postoperative day with dilated, fixed pupils.

Pathologic summary. A necrotic tumor mass 4 x 4 x 3 cm. in size was seen in the right temporal lobe. Elsewhere, the outer surface of the brain was not unusual. The tumor was not distinct from brain tissue on section. It obliterated the right inferior horn of the lateral ventricle and a small part of the right globus pallidus. The right lateral ventricle was smaller than the left, and the third ventricle was displaced to the left. In the floor of the anterior horn of the left lateral ventricle, the ependyma was replaced by a mass of tumor tissue and under the ependyma on the lateral wall was a nodular firm mass 3 mm. in diameter. A 1-cm. mass was in the subependyma of the right anterior horn but was not sharply demarcated from surrounding brain tissue. Anatomic diagnoses included glioblastoma multiforme, right temporal lobe and anterior horns of both lateral ventricles; meningitis, acute, purulent; and epidural hematoma.

Comment. Since the midportion of the anterior horns of the lateral ventricles course through deep parietal lobe, it is seen from the

pathologic summary that parietal lobe involvement almost certainly occurred in this case, in which a positive optokinetic nystagmus sign was seen.

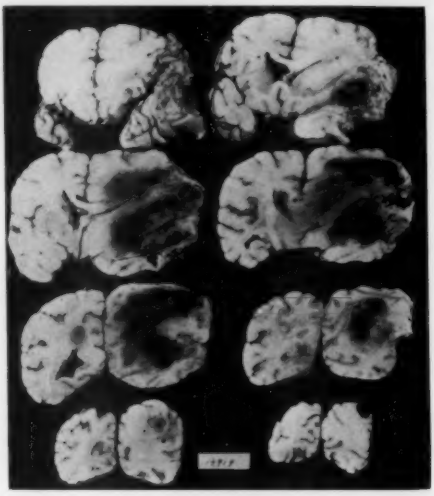

Fig. 5. Case 9

Case 9. A-14919. *Clinical summary.* This 38-year-old white male had bifrontal headaches and difficulty with speech for three weeks. Not only did he have difficulty in expressing himself, but for two weeks his wife thought he was becoming deaf, as he appeared unable to comprehend what was said to him. On examination, a receptive aphasia, diminished perception of pinprick over the entire right side of the body, and a right supranuclear facial weakness were noted. Papilledema, anisocoria with the left pupil larger, and a right homonymous hemianopia were present. Skull films revealed a pineal shift to the right. At left temporal craniotomy, tumor was encountered presenting on the surface beneath the terminal portion of the sylvian vessels. A partial resection was performed, as the tumor extended deeply into the thalamus. The patient was discharged with a diagnosis of left temporoparietal glioblastoma multiforme.

Three months later, he was readmitted with right-sided weakness and a global aphasia. Ophthalmologic examination revealed vision in the right eye limited to hand movements at 1 ft. and in the left eye, to finger counting at 18 ft. An exotropia was present, but motility was full. The right pupil reacted poorly to light. Bilateral papilledema was present, and there was a complete retinal separation in the right eye. A dense right homonymous hemianopia was present. The eyes deviated to the right on lid closure. A positive optokinetic nystagmus sign was present, with a good response to the right but minimal to the left. Repeat craniotomy disclosed a massive neoplasm with little normal brain tissue visible. The patient was discharged with a spastic right hemiplegia, right hemianesthesia, aphasia, and right Babinski response. He died quietly at home five months later.

Pathologic summary (Fig. 5). The left hemisphere was markedly enlarged and distorted with fragmentation, particularly of the temporal lobe. Convolutional flattening was most marked on the left. On section, an extensive tumor mass involved almost the entire left hemisphere. In the parietal cortex, a round cystic area, 2.5 cm. in diameter and filled with greenish coagulum, was seen. The tumor extended anteriorly to posterior frontal lobe, was most extensive in temporal and parietal lobes, and extended posteriorly to within 2 cm. of the occipital lobe. In the parietal region, the ventricular space on the left was completely obliterated and that on the right was narrowed by compression. In this area, the tumor involved the corpus callosum and extended across the midline into the right hemisphere for 2.5 cm. The thalamus was obscured on the left by tumor. Cerebellum, brain stem, and midbrain were normal on section. Anatomic diagnoses included glioblastoma multiforme, left hemisphere, with extension to corpus callosum and right hemisphere.

Comment. This glioblastoma involved almost the entire left hemisphere and was most extensive in the thalamus and temporal and parietal lobes. A positive optokinetic nystagmus sign was noted.

Case 10. A-16103. *Clinical summary.* A 63-year-old white woman was admitted because of abrupt onset of a global aphasia. Examination revealed arteriosclerotic heart disease with auricular fibrillation. On neurologic examination, slight flattening of the right nasolabial fold was the only abnormality otherwise. Eye examination revealed 14/35 vision in both eyes, but the aphasia made testing difficult. Confrontation fields were said to be full. The optokinetic responses were normal. The aphasia cleared progressively; three months later, the patient consulted an ophthalmologist, stating that difficulty in reading had persisted following the stroke. Vision was 20/20 in both eyes, and the fundi were normal. A slightly incongruous right homonymous hemianopia was noted (3/1,000 white). A repeat examination fourteen months later disclosed no change in this field defect. Four months later, because of a right facial weakness of several days' duration, she was readmitted. In addition to a complete right peripheral facial palsy, examination revealed cerebellar ataxia on the right. Eye examination now revealed 15/20 vision in both eyes and nystagmus with rapid component to the right, and the right homonymous hemianopia

Fig. 6. Case 11

persisted as before. A positive optokinetic nystagmus sign was now noted—the response was defective to her left and intact but faulty to her right. Deafness was noted in the right ear, and involvement of the right seventh and eighth nerves pointed to a brain stem lesion. The right corneal reflex later disappeared while she was on anticoagulant therapy. On the forty-first hospital day, posterior fossa exploration was carried out and a tumor of the right cerebellar hemisphere was partially removed. She died on the sixtieth day.

Pathologic summary. Minimal atherosclerosis of vessels was noted at the base. Externally, 2 lesions were visible, 1 a large defect in the right cerebellar hemisphere. Gray firm tissue was overlying the cerebellum and adherent to the fifth, seventh, and eighth nerves. The pons and cerebellopontine angle were implicated by thickened leptomeninges. Coronal sections revealed that the right brachium pontis, right side of pons, and adjacent cerebellar cortex were discolored by a red-gray neoplasm. These changes extended vertically from upper to lower pons but were most marked at lower level.

An extensive defect involved most of the left superior temporal gyrus, extending from the anterior portion of the sylvian fissure posteriorly to the occipital lobe. The entire superior gyrus was atrophic. Multiple sections confirmed the extent of the lesion, and, posteriorly, the lateral occipital cortex and subcortical white matter and cortex of the fusiform gyrus were similarly altered. In the temporal lobe, the lesion extended to within 3 mm. of the posterior horn of the lateral ventricle and the optic radiation appeared involved. No other lesions were seen on gross examination of the brain. Anatomic diagnoses were medulloblastoma, right cerebellum; cerebral infarct, left parietal region (twenty months old); and rheumatic heart disease.

Comment. This case is difficult to interpret because of the presence of 2 lesions affecting the efferent optomotor pathways—an old left parietal infarct secondary to embolism from auricular fibrillation and a more recent cerebellar medulloblastoma. Initially, a normal optokinetic response was present, as well as full confrontation fields. However, perimetry disclosed a right homonymous hemianopia that remained unchanged on 3 examinations during the next year and a half. At the last admission, the optokinetic response was defective to the left and present, but faulty, to the right. Several possibilities exist: [1] the hemianopia and positive O.N. sign may have developed in the three-month interval between the first hospitalization and detection of the field defect, or [2] both of these may have been present at the initial embolic episode and may have been overlooked, since the patient was too ill for protracted examination. At any rate, a defective response to optokinetic targets from right to left was noted in this case, as well as a left parietal infarct.

Case 11. A-16371. *Clinical summary.* This 60-year-old white female had a sudden episode of aphasia and right hemiparesis two months before admission. This cleared rapidly, but a second episode a week before entry left her with a global aphasia. Examination revealed a mild right hemiparesis and right-sided hypalgesia in addition to the dysphasia. Ophthalmologic examination was limited because of the aphasia, and visual fields could not be done. However, there was a definitely poor optokinetic response to the left. Ophthalmodynamometry disclosed equal diastolic pressures in the 2 eyes. The fundi were normal. She improved silghtly but was readmitted two and one-half weeks later in semicoma. Eye examination now revealed a tendency toward conjugate deviation to the left, and early papilledema was present. The patient died two davs later.

Pathologic summary (Fig. 6). A discrete tumor occupied the left frontal and parietal lobes, measuring 6 x 12 x 3 cm., and extended from a point 3.4 cm. from the frontal pole back to the plane of midthalamus. It lay above the plane of the sylvian fissure and extended medially as far as the insula. For the most part, this lesion was sharply demarcated from the surrounding edematous centrum semiovale. Horizontal sections through the brain stem revealed compression of the right crus and a slit hemorrhage in the basis pontis. Anatomic diagnoses included glioblastoma multiforme, left frontal and parietal lobes, and Cushing's ulcer.

Comment. This patient with a neoplasm in the inferior frontal gyrus presented an asymmetric optokinetic response. At autopsy, defi-

nite extension into the parietal lobe was observed.

Case 12. A-17968. *Clinical summary.* This 28-year-old white female was in good health until three years before entry, when she noted a mole growing in her back. This recurred after electrocautery treatment, and a year and a half later, a wide excision was performed. A short time later, still another and wider excision was carried out, and the family was informed that this was a malignant melanoma. Two days before admission, she developed headaches and vomiting; she had had a seizure four days before admission. She had also noted recent sensation of dragging the left foot.

Examination revealed a mildly confused woman giving inappropriate answers. The only other abnormalities noted were decreased strength in the left lower extremity and a left Babinski response. Ophthalmologic examination was negative. In particular, the visual fields were full, there was no spasticity of conjugate gaze, and optokinetic nystagmus was equal to both sides. The patient failed rapidly and died on the sixth hospital day.

Pathologic summary (Fig. 7). In the external surface of the brain, 3 large metastatic lesions were seen. The largest was in the left posterior parietal region and measured 2.5 x 1.5 cm. It was firm and brown, and the surrounding white matter was swollen. The cortex did not appear to be involved. The white matter was severely edematous. Similar metastases were found on medial surface of right frontal lobe and in the right posterior temporal region. No other abnormalities were found in the brain. The brain stem and cerebellum were normal. Anatomic diagnoses included malignant melanoma, metastatic to brain, and cerebral edema, marked, secondary, with temporal and cerebellar pressure cones.

Comment. This case revealed a definite left parietal metastasis of a malignant melanoma, and yet no defect was present in either visual fields or optokinetic nystagmus. It is possible that death occurred too rapidly for clinical manifestations of these lesions. The extent of a cerebral neoplasm cannot always be correlated with the functional manifestations noted. If a hemianopia had been present with this lesion and yet a negative O.N. sign was noted, it would have been a much more difficult case to reconcile than if no abnormalities had yet appeared.

Case 13. A-19344. *Clinical summary.* This 54-year-old white male noted numbness of the right hand and leg three months before admission. Sometime later, he noted poor vision to the right. Examination revealed diminished pinprick over the right side of the body and face but normal tactile sensation. Ophthalmologic examination revealed intact corneal sensation, but a complete right homonymous hemianopia was detected with apparent splitting of fixation. The optokinetic response was defective on rotating the drum to the patient's left. Ophthalmodynamometry disclosed equal diastolic pressures in the 2 eyes. A ventriculogram was negative.

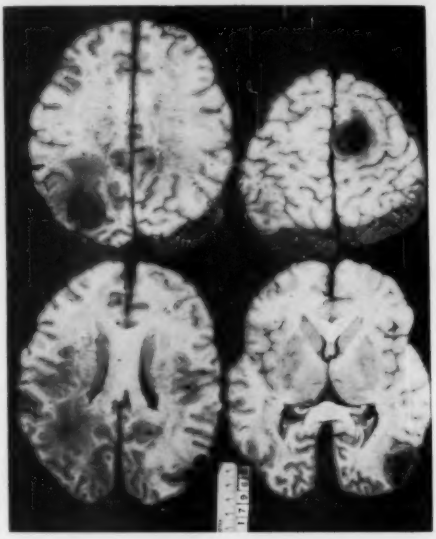

Fig. 7. Case 12

Two years later, the patient was admitted with signs of progressive bulbar ischemia, including cortical blindness, dysphagia, and dysarthria. Despite anticoagulant therapy, progressive bulbar signs occurred during the final two years before his death.

Pathologic summary. The brain weighed 1,310 gm. Advanced atherosclerosis of the vertebral-basilar system was present, and, on section, the basilar artery was totally occluded below the exit of the superior cerebellar arteries. Both posterior cerebral arteries were likewise totally occluded 1.8 cm. distal to their origin from the basilar. Extensive softening was noted in both peduncles, midbrain, and upper pons, as well as both cerebellar hemispheres. In the left occipital lobe, extensive softening extended posteriorly to the pole; similar but more recent appearing softening was noted in the right occipital lobe. The right anterior cerebral and a secondary branch of the left middle cerebral artery were both virtually occluded as well. An extensive lesion was seen in the left hippocampal gyrus, and massive necrosis of the thalami was present. Several lacunae were seen above the left lateral geniculate body. Scattered softenings were noted in the left superior parietal

lobule and middle temporal gyrus, confined to the cortex. Anatomic diagnoses included basilar artery thrombosis and bilateral posterior cerebral artery thrombosis.

Comment. This patient had progressive atheromatous disease of the basilar system, as well as bilateral posterior cerebral occlusions. The clinical history and anatomic findings supported early involvement of the left posterior cerebral artery. The optokinetic nystagmus sign had been positive early, only three months after onset of symptoms. Since a secondary branch of the left middle cerebral artery was also occluded, it cannot be said with certainty whether the optokinetic asymmetry was due to left middle or posterior cerebral artery disease. Certainly, with the extensive basilar thrombosis later, the efferent optomotors in the brain stem were so compromised that no conclusions about cortical localization from optokinetic response could be drawn. The left parietal lobe was involved in this case.

Case 14. A-13657. *Clinical summary.* This 45-year-old white male was admitted because of headaches for three weeks. A blood pressure of 195/105, slight edema of the lids, anisocoria, ptosis on the right, and nystagmus were the only positive findings. Vision was recorded as 14/84 on the right and 14/168 on the left. Confrontation fields were full. One month later, the patient suddenly became unable to see. Examination then revealed normal pupils and fundi, with nystagmus on both right and left lateral gaze. Eleven hours later, an ophthalmologist found that he could count fingers at 2 ft. with each eye, and a right homonymous hemianopia was noted. On optokinetic testing, the patient appreciated movement of the drum and correctly named the direction but denied ability to make out the markings. The examiner wrote that "this would seem to be confirmed in that no nystagmus could be elicited." By the following day, he could count fingers at 4 ft. with each eye. Full visual fields (2/330 and 10/1,000 white) had then returned. Optokinetic testing again revealed a complete absence of the normal response to both right and left directions. Impression was cortical blindness, transient, and a right Horner's syndrome. The headaches could not be controlled; the patient began to have convulsions, had a severe aphasia, and went into coma one day before death.

Pathologic summary. Small scattered lesions were encountered throughout the brain. Some slightly larger lesions were found in the deep layers of the right occipitoparietal cortex, which had the appearance of relatively recent infarcts. Several small arteries in this region were surrounded by a clear zone of eosinophilic material and had a markedly proliferated endothelium. Similar changes were pronounced in the cerebellum. Anatomic diagnoses included thrombosis of right renal and superior mesenteric arteries, with impending infarction of right kidney, and encephalopathy, type and cause unknown, probably vascular.

Comment. This 45-year-old man presented a diffuse vascular disease of unknown cause, which caused death within eight weeks of onset. He had definite cortical blindness, with a right homonymous hemianopia noted as the blindness cleared. Within twenty-four hours, the fields were normal. Despite cooperation, no optokinetic response could be elicited to either side during the period of amaurosis or thereafter, despite his ability to tell correctly the side of rotation. Lesions were seen in the right parietal lobe. The left parietal lobe was not studied histologically. A similar process there appears likely because of the diffuse nature of this disease process.

DISCUSSION

Clinical experience with cases of cerebrovascular disease suggests that a positive optokinetic nystagmus sign indicates parietal lobe disease. The present anatomic evidence substantiates this impression. A symmetric optokinetic response was elicited to both sides in 3 of the autopsied cases (Cases 3, 4, and 6). These had lesions of temporal, occipital, and frontal lobes, respectively, with no parietal involvement. Of the autopsied cases, 6 had positive (asymmetric) optokinetic nystagmus signs, and parietal lobe involvement was present in each (Cases 1, 2, 5, 7, 9, and 11). However, 5 of the cases present difficulties in interpretation. Thus, Cases 10 and 13 both have dual lesions (basilar artery thrombosis and cerebellar medulloblastoma in Case 10). Case 12 had a left parietal metastatic malignant melanoma, and yet normal visual fields and optokinetic nystagmus were found clinically. This patient died from massive cerebral edema within ten days of onset of neurologic symptoms, and perhaps death occurred too rapidly for clinical manifestations of the lesions. The fact that no field defect was present in this case favors the fact that there was little evidence of parietal dysfunction present at time of admission. Case 8 is a temporal lobe neoplasm with an asymmetric optokinetic nystagmus sign. However, parietal lobe extension probably occurred in this case, and further

anatomic study would have been helpful. Finally, the same factor arises in Case 14, in which only 1 parietal lobe was studied histologically.

The method of testing was rotation, at a moderate rate, of a large optokinetic drum held about 20 in. from the patient. This was done several times to both sides in order to compare the responses. It should be noted that slight asymmetry may be seen at times in normal persons. Only either an absent response to 1 side or a definitely defective, asymmetric response should be called a "positive O.N. sign." An absent response to both sides has little diagnostic significance. The most common causes for this finding are that the patient is obtunded or sedated, has very low vision, or is ignoring the test. It should be noted that optokinetic nystagmus has been found to be variable in lateralization of brain stem disease in the experience of Dr. Cogan, so that the statements made previously apply to its use only in cerebral lesions. Vertical optokinetic responses were not interpreted in this study.

SUMMARY

The optokinetic response was analyzed in 14 cases of cerebral disease that came to autopsy examination; 6 of these cases had positive (asymmetric) optokinetic nystagmus signs and were found to have parietal lobe lesions. Lesions of temporal, occipital, and frontal lobes were found in 3 cases, respectively, with no parietal involvement. The optokinetic nystagmus sign was negative in these cases. Complicating factors in interpretation of the other 5 cases have been discussed.

A frequent occurrence noted in cases with positive optokinetic nystagmus signs was concomitant involvement of the thalamus. This would not be unexpected with lesions involving the middle and posterior one-third of the optic radiations, deep in the posteroinferomedial parietal lobe. It is concluded that a positive optokinetic nystagmus sign in cortical lesions is most suggestive of involvement of the parietal lobe.

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The subcommissural organ

Gordon J. Gilbert, M.D.

EVEN in its anatomy, the midbrain is incompletely understood. There is in the literature no description of the subcommissural organ in man, though it has been well described and studied in vertebrates at all stages of evolution, from the lowest fishes to the monkey.[1] It is a small structure, probably of ependymal derivation, consisting of elongated secretory cells lining the anteroinferior surface of the posterior commissure. From the cells of the subcommissural organ arise minute fibrils that unite within the cerebral aqueduct to form Reissner's fiber,[2] a delicate strand completely encompassed by the cerebrospinal fluid and extending caudally from the subcommissural organ to the inferior termination of the spinal canal. Using histochemical technics, Wislocki and Leduc[3] were able to demonstrate that, in the rat, the subcommissural organ is the site of an extraordinary level of enzymatic activity and produces a secretion that extends from the nucleus to the lumenal surface. This secretion appears to be remarkably similar in its histochemical properties to the material stored within the posterior pituitary.

It seemed reasonable to postulate that, like the neurohypophysis, the subcommissural organ might be concerned with water metabolism. In an early investigation,[4] the author attempted the microcoagulation of the subcommissural organ in 46 white rats, of both sexes, weighing 200 to 250 gm. Postoperatively, the animals were observed daily for at least two weeks, when possible. Often, however, the postoperative fall in water consumption was such that the rats' weight loss became severe within four or five days, necessitating earlier sacrifice. Careful postmortem examination of each brain was performed and the presence or absence of the subcommissural organ noted, as were the size and location of the lesion. It was found that, in each animal with a subcommissural organ completely destroyed by electrocoagulation, an immediate, drastic, and persisting fall in water consumption occurred, death ensuing within a few days. In the rats with water consumption unaffected by the operation, microscopic examination revealed the subcommissural organ to be intact. Partial destruction of the subcommissural organ was associated with an initial fall in water consumption, which returned to normal levels within a few days. In 2 rats that manifested increased water intake on the day of the operation and normal levels thereafter, the subcommissural organ was found intact but the lesion was very close to it. It was postulated that, in these 2 animals, an electrical stimulation of the organ had occurred.

A second experimental procedure[4] was designed to ascertain whether the subcommissural secretion possesses hormonal activity with influence on water metabolism. Isotonic saline extracts of rat subcommissural area were prepared and injected subcutaneously into rats. Because of the great difficulty encountered in keeping alive rats with destroyed subcommissural organs, the rats used in this investigation were normal healthy animals. A uniform fall in water consumption, averaging 20%, was noted on the day of the subcommissural injections; extracts prepared from rat cerebrum were without effect on water intake.

A working hypothesis was elaborated. It was felt that the subcommissural organ might function in the regulation of body fluid volume. Responding to a depletion in body water, the organ could initiate a reflex arc in the contiguous brain stem and hypothalamus to promote increased consumption. Simultaneously, a hormone manufactured and released

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by the activated subcommissural organ would act at the renal level so as to conserve fluid in the depleted animal. The hormones secreted by many of the endocrine glands possess the property of depressing the activity of the parent gland. By ascribing such a function to the subcommissural secretion, we were able to explain the depression of water consumption after the injection of subcommissural extracts into the normal white rat.

Our hypothesis (that the subcommissural organ functions in the regulation of body water volume) led us to seek in the subcommissural organ an anatomic correlate to changes in the state of hydration of the living animal. An experiment was performed[5] in which 6 white rats were dehydrated over a period of seven to thirteen days and their brains stained with periodic acid–Schiff, which selectively stains the secretion of the subcommissural organ. The subcommissural organs of these rats were then compared with those of well hydrated animals. The subcommissural organ of the dehydrated rat was found to possess a far greater affinity for periodic acid–Schiff than did the organ of the well hydrated rat.

Our next objective was to identify more clearly the active principle contained within the subcommissural secretion. It was felt that the similar chemical affinities of the neurohypophyseal and subcommissural secretions might denote a close biochemical relationship. Wislocki and Leduc[3] had demonstrated that the chrome alum hematoxylin stain has a strong affinity for each of these secretions. Developed by Gomori as a specific stain for the beta cells of the islets of Langerhans, chrome alum hematoxylin had been regarded as a selective stain for insulin, a protein of molecular weight 34,000. It has since been shown by Hild and Zetler[6] that the material contained within the neurohypophysis and having an affinity for Gomori's stain is actually the protein precursor from which the octapeptides oxytocin and vasopressin are derived. Histochemical methods suggested, then, that the subcommissural secretion might be a protein.

In order to test this hypothesis, we extracted beef subcommissural organ, employing a number of different solvents.[7] The extracted material was centrifuged and the supernatant injected subcutaneously into a rat; daily water consumption then was carefully measured. Aqueous extracts of beef subcommissural organ were found to depress water consumption in the injected rat over the following twenty-four-hour period, while aqueous extracts of beef pulvinar were without effect on water intake. Since 0.25% acetic acid is employed widely in the extraction of the octapeptides from whole posterior pituitary, it was used in the extraction of the subcommissural organ. These acetic acid extracts were found to be without effect upon the water consumption of the injected rats. The destruction of subcommissural activity by dilute acetic acid offers support to our concept of a protein hormone. Our efforts to fractionate the aqueous extracts by shaking with ether or petroleum ether resulted in the total loss of activity in all fractions.[7] Since proteins may be denatured by shaking, this property, too, suggests that the active principle is not a polypeptide but may be a labile protein molecule.

In view of these remarkable properties of the subcommissural organ in the rat, the problem of whether it exists in adult man is indeed intriguing. There has been one earlier study. In 1910, Dendy and Nicholls[8] prepared sections through the upper midbrain of a single adult human subject of undisclosed age and sex. They did not find the "elongatedly columnar epithelium" that they felt to be characteristic of the subcommissural organ in lower types and concluded that the subcommissural organ is absent in man. Their conclusion has been generally accepted and quoted in neuroanatomic literature over the last forty-eight years.[9]

The more recent development of histochemical technics that permit the selective staining of the subcommissural secretion[3] would appear to provide a more precise method for determining the presence or absence of a secretory subcommissural organ in the adult human brain.

METHOD

Used in this study were human brains coming to autopsy at the West Haven Veterans Administration Hospital during the autumn months of 1958. Shortly after death, all brains had been fixed in formalin, in which they remained for approximately one week before

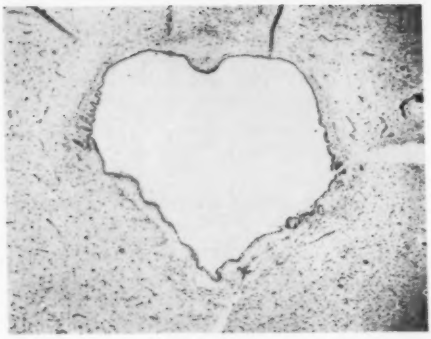

Figure 1

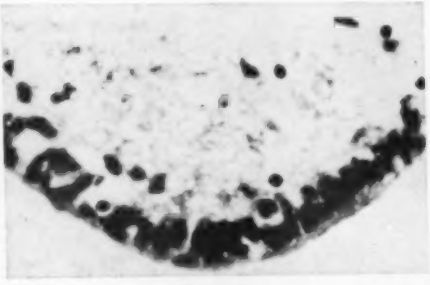

Figure 2

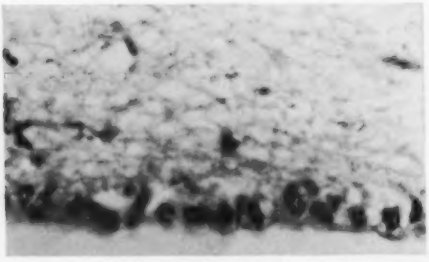

Figure 3

sectioning. The midbrain was then removed, embedded in paraffin, sectioned transversely or saggitally (6μ), stained with periodic acid–Schiff, counterstained with hematoxylin, and studied microscopically.

RESULTS

In this study, 9 adult human brains were examined, and in each of these a secretory subcommissural organ was found. The ages of these brains were, respectively, 30, 49, 63, 64, 64, 67, 68, 74, and 75 years; 1 of the 64-year-old brains was that of a female; all others were from males.

A considerable amount of individual variation was seen in the configuration of the subcommissural organ as viewed on cross section. Most commonly, however, the subcommissural organ took the form of a single promontory bulging into the cerebral aqueduct from its roof. This type of structure in the brain of a 49-year-old male is illustrated (x 40) in Figure 1. At higher power (x 750) in Figure 2, the characteristic secretory cells are seen. Periodic acid–Schiff–positive secretory material extends from the basally located nuclei to the lumenal surface. This can be compared with Figure 3, a section of ependyma lining the lateral wall of the cerebral aqueduct at the same transverse level. These nuclei are not basally located, nor is there evidence of a peripheral Schiff-positive secretion.

Figure 4 reveals a paired subcommissural organ (x 53), found in only 1 brain, that of a 64-year-old female. A similar doubling of the organ has been described in 1 human fetal brain.[10] The typical secretion is again demonstrated in Figure 5.

Yet another variation in subcommissural morphology is illustrated in the 68-year-old male brain in Figure 6. A narrow groove extends down the center of the upper aqueductal roof, and around this groove cluster the strongly secretory subcommissural cells. Their nuclei are large, basally located, and elongate in a plane perpendicular to the surface. Secretory material extends from the nuclei to the margin of the groove.

DISCUSSION

The "elongatedly columnar epithelium" sought in vain by Dendy and Nicholls in their specimen was equally inapparent in our material. It is evident that the subcommissural cells have become squat in man, but it is equally clear that a subcommissural organ is indeed present in the adult human brain. The degree of secretory activity seen in our sections is comparable to that noted in the rat, in which destruction of the subcommissural organ creates fatal havoc in fluid balance.

In man, disease of the brain stem can be

associated with severe disturbances of fluid and electrolyte balance, including "cerebral salt wasting," "cerebral salt retention," and dehydration. The renal mediation of the cerebral salt syndromes suggests an endocrine mechanism, and a "volume receptor," located intracranially, has been postulated.[11,12] It is possible that the volume receptor is to be found in this organ composed of secretory cells coating the ventral surface of the posterior commissure. A frequent concomitant of midbrain disease is impairment of consciousness, which renders difficult the evaluation of such disturbances as adipsia and electrolyte imbalance. The general recognition of the existence of a subcommissural organ in man and of its pronounced effects on fluid balance in lower animals might, however, promote attempts to correlate fluid-electrolyte abnormalities in cases of midbrain disease and subcommissural organ pathology.

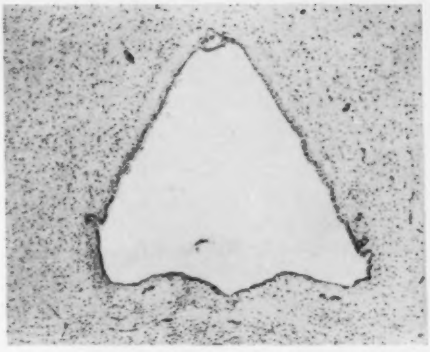

Figure 4

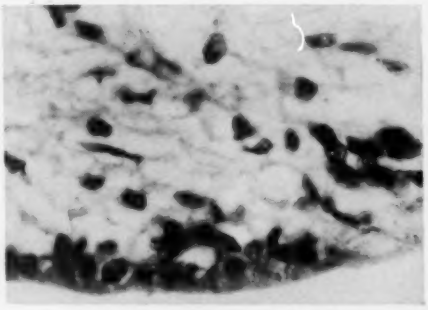

Figure 5

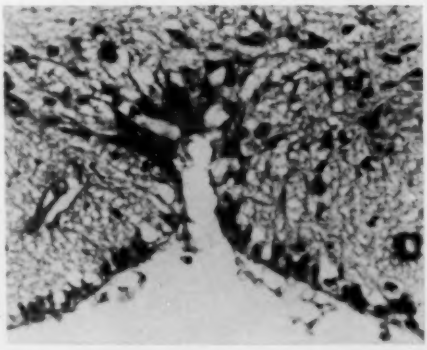

Figure 6

ADDENDUM

In attempting to localize the cerebral regulation of adrenal aldosterone, Farrell and associates[13] have found that lesions of the periaqueductal gray involving the posterior commissure markedly depress aldosterone secretion. In saline extracts,[14] aldosterone-stimulating activity was highest in the "pineal complex," consisting of the pineal and the anterior portion of the posterior commissure (where the subcommissural organ is located); Farrell found, as we did in our subcommissural extracts, that cold extraction was necessary to obtain optimal hormonal activity. Thus, fluid retention by the postulated subcommissural volume receptor may be mediated via adrenal aldosterone stimulation, resulting in the renal retention of salt water. By directly stimulating thirst, the subcommissural organ would further increase fluid volume in the depleted animal. Aldosterone determinations should prove of great interest in the cerebral salt retaining and wasting syndromes.

SUMMARY

The subcommissural organ is located at the anteroinferior surface of the posterior commissure. Histochemical studies suggest that the organ possesses secretory activity. Its electrocoagulative ablation in rats results in an immediate and drastic fall in water consumption,

while the subcutaneous injection of its aqueous extract into rats is followed by a sharp alteration in water intake. The subcommissural organ of the dehydrated rat possesses a greatly increased quantity of periodic acid-Schiff-positive secretory material. It is suggested that the subcommissural organ may be the so-called volume receptor of the body, regulating the total body fluid content. The existence of a subcommissural organ in the adult human brain has been previously unrecognized. Using periodic acid–Schiff staining technic, we find a secretory subcommissural organ present in each of the 9 adult human brains studied.

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Cholesterol and fatty acid synthesis in diabetic nerve and spinal cord

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Diabetes mellitus may be accompanied or even preceded by neurologic symptoms.[1] The clinical incidence of diabetic neuropathy as given by different authors varies considerably.[2] In part, this is due to the difference in criteria used to establish the diagnosis. The factors leading to the development of neuropathy are, at the present time, unknown. Theories that have been proposed to explain diabetic neuropathy favor either a vascular[3] or metabolic[4] genesis. Experimental diabetes has been of little value in the study of diabetic neuropathy in that neurologic symptoms are rare.[5] A well known metabolic disturbance in experimental diabetes is depression of fatty acid and cholesterol synthesis in liver.[6–8] Siperstein and Fagan[8] studied the enzymatic factors involved in the depression of lipogenesis and found that addition of reduced triphosphopyridine nucleotide (TPNH) corrected the defect. From this, they deduced that reduced glucose oxidation via the hexosemonophosphate pathway, normally the source of TPNH, would put a rate limitation on lipogenesis. Synthesis of fatty acids and cholesterol plays a major role in the formation and maintenance of the myelin sheath. It was therefore thought to be of interest to investigate the ability of the nervous tissue from alloxanized rats to incorporate acetate-1-C^{14} into lipids. We also studied the effect of additions of diphosphopyridine nucleotide (DPN) and TPN on lipogenesis in nerve and spinal cord from both normal and diabetic rats.

METHODS

Animals. Sprague-Dawley rats weighing 250 to 400 gm., from the Holtzman Rat Company, Houston, were used for this study. They were maintained on Purina Laboratory Chow. Diabetes was induced by intraperitoneal injection of 100 mg. of alloxan monohydrate per kilogram of body weight. The alloxan was buffered as described by Klebanoff and Greenbaum.[9] The diabetic rats were used within one to four weeks after injection and had fasting blood sugars exceeding 250 mg. per cent and a urinary output of over 200 cc. Rats that had been injected but did not become diabetic were used as controls on the effect of alloxan injections.

Preparation. The animals were killed by a blow on the head and the sciatic nerve and spinal cords rapidly removed and placed in Krebs buffer. Fat and connective tissue were removed and the nerve and spinal cord cut into 3-mm. segments and weighed. The nerve tissue fragments were placed in center-well flasks of Baruch's type,[10] and substrates, coenzymes, and acetate-1-C^{14} were added to a total volume of 1.45 cc. or 2.45 cc. The flasks were gassed with 95% oxygen and 5% carbon dioxide for ten seconds and incubated at 37.5° C. for two hours in a Dubnoff shaker.

Analytical methods. The methods used are extensively described by Siperstein and Fagan.[11] After incubation, carbon dioxide was removed from the center well by shaking the flasks for thirty minutes in an ice bath with alkaline hyamine 10 X 1-1 methanol-toluene[12] in the center well. The hyamine solution was mounted with toluene and diphenyloxazole and the radioactivity assayed in a Packard Liquid Scintillation Counter. Saponification of the remaining solution with 1 cc. of 90% po-

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TABLE 1

INCORPORATION OF ACETATE-1-C^{14} INTO CHOLESTEROL IN $m\mu M \times 10^{-2}$ PER 100 MG. OF FRESH TISSUE

A. *Spinal cord*

Experiment	*I*	*II*	*III*	*IV*	*V*
Normal	60	9	93	18	100
Diabetic	20	52	68	5	15

B. *Sciatic nerve*

Experiment	*I*	*II*	*III*	*IV*	*V*
Normal	360	310	205	274	183
Diabetic	100	80	66	68	110

Concentrations of additions: Glucose-6-phosphate, 16×10^{-3} M; potassium acetate, 1.6×10^{-3} M
Total volume, 2.45 cc.

tassium hydroxide brought the nerve fragment into solution. The nonsaponifiable material was extracted with petroleum ether and the cholesterol fraction isolated as digitonide.[13] The digitonide was dissolved in methanol and then added to the scintillation solution and counted. The saponified material was dissolved in ethanol; the ethanol was then evaporated and water added to the mixture. After acidification, a petroleum ether extract was prepared, an aliquot of which was assayed for fatty acid-C^{14}.

RESULTS

Effect of alloxan-induced diabetes on nerve lipogenesis. Glucose-6-phosphate (Sigma Chemical Company) was used as glycolytic substrate to study the incorporation of acetate in nerves and spinal cord of normal and diabetic animals. The results as given in Table 1 show an incorporation of acetate by normal nerve into cholesterol in amounts ranging from 183 to 360 $m\mu M \times 10^{-2}$. In contrast, only 66 to 110 $m\mu M \times 10^{-2}$ of acetate are incorporated in the cholesterol of the diabetic nerve. This decrease in incorporation is independent of the length of time the animal has been diabetic and of its blood sugar level present one week after alloxan.

The depression in diabetic nerve cholesterol synthesis amounts to almost 80% in most instances. In contrast, in the same animal, the spinal cord cholesterol synthesis is only depressed by about 40% (Table 1). In 1 experiment, the synthesis of cholesterol in the diabetic cord was higher than in the normal cord.

It is apparent, therefore, that, with the use of glucose-6-phosphate as glycolytic substrate, the incorporation of acetate-1-C^{14} into cholesterol from the nerves and spinal cords of diabetic animals is depressed.

The quantity of fatty acids synthesized in normal cord and nerve tissue varies from animal to animal. In the experiments reported in Table 2, a constant depression is seen in fatty acid synthesis in the spinal cord of diabetic animals. The depression is zero to sixty-six-fold. In contrast, the synthesis in the diabetic nerve is 2 to 19 times higher than in the normal nerve.

TABLE 2

INCORPORATION OF ACETATE-1-C^{14} INTO FATTY ACIDS IN $m\mu M$ PER 100 MG. OF FRESH TISSUE

A. *Spinal cord*

Experiment	*I*	*II*	*III*	*IV*	*V*
Normal	3	36	4.5	22	14
Diabetic	1	12	0.4	0.3	11

B. *Sciatic nerve*

Experiment	*I*	*II*	*III*	*IV*	*V*
Normal	2.8	3	1.2	0.4	13
Diabetic	6	16	6	7.6	23

Concentrations of additions are the same as those used in Table 1.

Effect of DPN and TPN on fatty acid and cholesterol synthesis. Addition of DPN and TPN to nerve fragments using glucose-6-phosphate as substrate should stimulate glycolysis along the Embden-Meyerhot and hexosemonophosphate pathways, respectively.[14,15] In the first case, this should lead to an increased production of reduced DPN and, in the latter case, to an increase in reduced TPN. Since it is known that TPNH is required in the synthesis of fatty acids[16] and since it is also known that addition of TPNH can correct the synthetic deficiencies in diabetic liver homogenate,[8] glucose oxidation was alternately stimulated by the addition of DPN and TPN to the metabolizing nerve fragments.

Tables 3 and 4 show the effects of cholesterol synthesis with the additions of DPN and TPN, individually and combined, to the nerve fragments. The addition of these cofactors

TABLE 3

EFFECT OF COFACTORS ON THE INCORPORATION OF ACETATE-1-C^{14} INTO CHOLESTEROL IN $M\mu M \times 10^{-2}$ PER 100 MG. OF FRESH TISSUE BY NORMAL AND DIABETIC NERVE TISSUE

	A. Normal nerve			B. Normal cord		
Additions	*Experiment I*	*Experiment II*	*Experiment III*	*Experiment I*	*Experiment II*	*Experiment III*
None	310	205	130	18	11	9
DPN	800	500	280	76	84	75
TPN	1050	370	320	53	45	145
DPN + TPN	1310	800	530	23	74	40
	C. Diabetic nerve			D. Diabetic cord		
Additions	*Experiment I*	*Experiment II*	*Experiment III*	*Experiment I*	*Experiment II*	*Experiment III*
None	75	50	90	5	1.5	1.2
DPN	50	70	110	11	1.8	2.0
TPN	90	54	110	12	2.0	2.0
DPN + TPN	76	40	140	12	2.0	2.6

Concentrations of additions: Glucose-6-phosphate, 18×10^{-3}M; DPN, 1.4×10^{-3}M; TPN, 1.4×10^{-3}M; potassium acetate, 2.1×10^{-3}M
Total volume, 2.45 cc.

caused a definite increase in cholesterol synthesis in both normal nerve and cord (Table 3), while they apparently have no stimulating effect at all on diabetic nerve and only a questionable effect on diabetic cord. Table 4 demonstrates the effect of these cofactors on fatty acid synthesis. Again, DPN and TPN individually cause a decided increase in fatty acid synthesis in normal nerves. A definite stimulation can also be seen in the normal cord. A combination of the cofactors has less stimulatory effect. However, in diabetic nerve and cord, no consistent pattern of either stimulation or depression can be found.

To test the possibility that fatty acid and cholesterol production may be proportional to carbon dioxide production, the radioactive carbon dioxide was determined. In Table 5, 4 representative sets of data are given, indicating no parallelity between radioactive carbon dioxide production and fatty acid or cholesterol synthesis.

Control experiments were also carried out with alloxanized animals that did not become diabetic after the first injection. These showed no abnormalities in lipid synthesis from acetate.

DISCUSSION

In vitro preparations of spinal cord and peripheral nerves from animals incorporate acetate-1-C^{14} into cholesterol and fatty acids.[17] The incorporation is normally slow in the adult

TABLE 4

EFFECT OF COFACTORS ON FATTY ACID SYNTHESIS IN $M\mu M$ PER 100 MG. OF FRESH TISSUE

	A. Normal nerve			B. Normal cord		
Additions	*Experiment I*	*Experiment II*	*Experiment III*	*Experiment I*	*Experiment II*	*Experiment III*
None	22	13.5	36	0.4	1.3	3
DPN	120	100	298	0.7	16	15
TPN	210	360	259	10	7	10
DPN + TPN	80	50	80	14	11	10
	C. Diabetic nerve			D. Diabetic cord		
Additions	*Experiment I*	*Experiment II*	*Experiment III*	*Experiment I*	*Experiment II*	*Experiment III*
None	7.6	23	16	3	11	12
DPN	4.7	31	9	6	16	6
TPN	10.4	35	8	9	8	8
DPN + TPN	1.8	13	27	8	21	6

Concentrations of additions are the same as those used in Table 3.

TABLE 5

INCORPORATION OF ACETATE-1-C^{14} INTO CARBON DIOXIDE, FATTY ACIDS, AND CHOLESTEROL

Tissue	CO_2 $m_\mu M$ per 100 mg.	Fatty acids $m_\mu M$ per 100 mg.	Cholesterol $m_\mu M \times 10^{-2}$ per 100 mg.
Normal nerve	510	13.5	183
Diabetic nerve	437	23.0	110
Normal cord	161	13.0	10.6
Diabetic cord	241	11.0	1.5

Concentrations of additions are the same as those used in Table 1.

animal.[18] It would seem likely that the synthesis of these lipids follows the same pattern in nerves as in liver. If this is the case, generalized metabolic diseases that affect liver synthesis of lipids could possibly also damage nerve lipid synthesis. In diabetes mellitus, liver fatty acid synthesis from acetate is depressed[6] and cholesterolgenesis is either depressed[7] or elevated.[19] These defects can be corrected by addition of TPNH[8] to the incubation medium (occasionally, DPNH[20]).

In our experiments, we compared the incorporation of acetate into cholesterol of nerves and cords from normal and diabetic animals. A lower level of cholesterolgenesis was found in the diabetic nerve tissues. This could be explained on the basis of a metabolic block similar to that in diabetic liver. If that was the case, addition of TPNH should correct the metabolic defect. Addition of 2 μM of TPN with glucose-6-phosphate as substrate did not increase the cholesterol synthesis.

The failure of TPNH to correct the metabolic defect in diabetic nerve tissue may be due to a permeability disturbance. Cholesterol genesis probably takes place in the Schwann cells,[21] which may undergo membrane changes in diabetes. The same reason may apply to the fact that addition of DPNH and combination of both factors were equally ineffective.

If the cofactors do reach the site of cholesterol synthesis, an increased destruction or a lack of the protein moiety of the enzymes may explain the absence of stimulatory effect. Brain tissue has sufficient nucleotidase to destroy DPN and TPN quite rapidly,[22] but, if this also is the case in cord and nerves, it is not known. We have seen a stimulatory action of the cofactors on normal nerve and cord and would therefore have to assume that diabetic tissue has a more active nucleotidase. Additions of nicotinamide did not change or enhance the pyridine nucleotide effect.[23]

Another possibility to be taken into consideration would be the requirement of a specific donor system for TPNH.[11,24] It seems most likely, however, that, in nerve tissue, which preferentially uses glucose as a substrate, the glucose-6-phosphate–TPN system should be adequate.

Fatty acid synthesis is important to the nervous system. Fatty acids enter into the production of sphingolipids as well as their mother substance sphingosine and also form an important part of the glycerophosphatides. Fatty acid synthesis in the liver is also depressed in diabetes, and, here again, the theories proposed to explain this defect concentrate on coenzyme defects.[8,20,25] Our results point to a depression of acetate incorporation into fatty acids in diabetic spinal cord but an increase in diabetic nerve, both as compared with normal nerve tissues. The difference is interesting inasmuch as we have observed compensatory increases in fatty acid production in peripheral nerve after trauma and localized this to the Schwann cell fraction,[26] which normally does not participate to any great extent in fatty acid synthesis. In preliminary experiments, we have also found that cell-free preparations of peripheral diabetic nerve show a decrease in fatty acid production, which is the same as in diabetic cord. One might hypothesize that fatty acid production is so much more important to the nerve than cholesterol production that, in addition to the normal synthesis in the axon, a reserve mechanism is available in the Schwann cell. Langdon's[25] observations indicating the requirement for TPNH fatty acid production specifically in the stage from crotonyl to butyryl-coenzyme A (CoA) led us to try additions of TPNH to the incubation bath. A moderate stimulatory action on fatty acid synthesis in normal nerve was found, but no effect at all on the diabetic nerve was seen. The explanations offered for the absence of action in the case of cholesterol synthesis may also be entertained in this case.

It is important to realize that the comparison between metabolic defects in diabetic liver

slices and diabetic nerve tissue may not be justified. For one thing, the stimulatory action of cofactors on normal liver preparations is much higher than anything we have seen in normal nerve tissue. Even if no direct relation could be demonstrated between the carbon dioxide production (reflecting Krebs cycle activity) and the lipid synthesis in our experiments, an increased production of acetyl-CoA could be sufficient explanation for the observed increase in lipogenesis and cholesterol synthesis in normal tissue. For this speaks the fact that both DPN and TPN seem to give the same amount of increase in incorporation of acetate. On the basis of these observations, we are inclined to doubt the importance of the activity in the hexosemonophosphate shunt and TPNH generation as controlling factors in nerve lipid synthesis.

SUMMARY

The incorporation of acetate-1-C^{14} into fatty acids and cholesterol of spinal cord and nerves was studied. Normal rats and rats made diabetic by alloxan injection were used.

In comparison with normal values, cholesterol synthesis is depressed in diabetic spinal cord and nerve.

Fatty acid synthesis is depressed in diabetic cord and elevated in diabetic peripheral nerve. Pyridine nucleotides stimulate lipogenesis and cholesterol synthesis in normal cord and nerve but do not influence the depressed production in the diabetic animal.

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Huntington's chorea in Michigan

III. Clinical observations

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AN INTEGRATED genetic and clinical study of all residents of Michigan known to be afflicted with Huntington's chorea during the period 1900 to 1955 has recently been completed; data used were obtained from a state-wide survey. Details of the methods used, along with an analysis of demographic and genetic data, have been published elsewhere,[1] as has a comprehensive discussion concerned with selection and mutation.[2] This, the third and final communication, will deal with certain clinical aspects of the disease.

In an attempt to obtain data on all persons known or reliably reported to have Huntington's chorea who had ever lived in Michigan, medically diagnosed propositi were obtained from several sources. The diagnostic files of the University Hospital and all the state hospitals in Michigan, as well as the files of the Veterans Administration hospitals in Michigan, the Wayne County General Hospital, and a number of county infirmaries, were reviewed in order to compile a listing of persons living or dead with definite or possible diagnoses of this disease. Kindreds already on file in the Heredity Clinic, Department of Human Genetics, of the University of Michigan were incorporated into the study. Pedigree data were gathered by field work and correspondence. Examination of new cases and nonaffected members of families was carried out in the University of Michigan Hospital Outpatient Department and in state hospitals and private homes. As a result, these genetic investigative facilities for ascertaining cases and gathering pedigree information have provided the clinical neurologist with the unique opportunity to examine a large number of patients with Huntington's chorea. They have also led to the discovery of the presence of Huntington's chorea in relatives not previously diagnosed and have provided for the examination of patients in the early stages of the disease long before these individuals would have normally sought medical care and advice.

Although the well-known description of this disease by George Huntington in 1872 called it to medical attention,[3] several accounts of hereditary chorea and dementia affecting adults had been reported prior to the publishing of this classic essay.[4–6] Among the important genetic investigations of the disease is that of Bell in 1934,[7] with geographic studies in Sweden by Sjögren in 1935;[8] the Rhineland (Germany) by Panse in 1942;[9] East Anglia,[10] the Duchy of Cornwall,[11] and Northamptonshire[12] in England; Victoria[13] and Tasmania[14] in Australia; Aichi Prefecture in Japan;[15] and the State of Minnesota in this country.[16]

The ancestry of some of the earliest known American families was discussed by Jelliffe[5] and Tilney.[17] Davenport and Muncey,[18] Vessie,[19] and Critchley[10] have traced the ancestry of a large number of cases to a small group of individuals who migrated to this country from Bures in Suffolk, England, around 1620. Davenport and Muncey, in 1916, stated that nearly 1,000 cases could be traced to about 6 individuals, including 2 (or 3) brothers from this small town. Critchley, in a later review, stated that there is no positive evidence that these men were brothers but did feel that they (and their wives) were undoubtedly related, probably by consanguinity. Other kindreds

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in the United States have been traced to France, Germany, England, Ireland, Norway, and other European countries,[20] as well as to countries outside continental Europe.

VITAL STATISTICS

A total of 229 kindreds having 801 affected members were gathered in our study. Of the 801 patients, 761 were established Michigan residents, the remainder being transients or residents of other states. Case records with pertinent data were tabulated for approximately 450 cases. An adequate neurologic examination was recorded for 325 and autopsy with neuropathologic findings compatible with Huntington's chorea was carried out on 60. Over a two-year period (1954-1955), 127 living choreics were examined during various stages of the disease.

The observed frequency of Huntington's chorea was determined for the Lower Peninsula of Michigan for April 1, 1940. As of that date, 203 individuals were found who were either medically diagnosed as having this disease or reliably reported to have it by lay sources, as well as having a close relative who was medically diagnosed. On the basis of a population of 4,932,562 (Lower Peninsula of Michigan, 1940 United States Census), accordingly, there was an observed frequency of 4.12 cases per 100,000 population, or about 1 choreic per 24,300 individuals. As of the same date, it was estimated that the frequency of individuals heterozygous for the dominant gene for Huntington's chorea was 10.1 per 100,000 population. The comparative frequency ranges of this disease that have been reported elsewhere are as follows: Rhineland, Germany, 3.22 per 100,000;[9] Cornwall, England, 5.57 per 100,000;[11] Northamptonshire, England, 6.5 per 100,000;[12] Minnesota, 5.43 per 100,000;[16] Victoria, Australia, 2.3 per 100,000,[13] and Aichi Prefecture, Japan, 0.33 per 100,000.[15] None of these studies is exactly comparable to the present investigation. If one can assume that the frequency of Huntington's chorea in Michigan was the same during the period 1954-1955 as it was in 1940 (1 choreic per 24,300 persons), with an estimated census on the later date of 6,500,000, one could postulate that there were 267 living choreics. Inasmuch as 127 were examined, approximately 50% of those living were seen and examined.

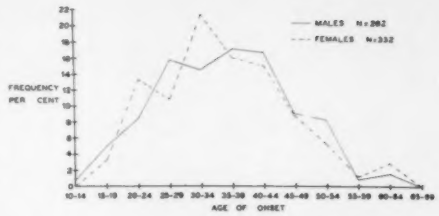

Fig. 1. Age at onset of symptoms in 614 patients with Huntington's chorea in whom the time of onset could be definitely established

Of the 761 Michigan residents with Huntington's chorea, 363 were male and 398 were female. The exact age of onset was often difficult to determine, since there frequently were discrepancies in statements of equally reliable observers. In the main, the age of onset was considered to be the time of appearance of choreiform movements, but, on occasion, the time was determined on the basis of the appearance of definite mental or emotional changes prior to the appearance of movements. Using these criteria, the range of age of onset of symptoms of the disease was 15 to 65 years, with a mean age of onset of 35.3 years (Fig. 1). This mean agrees closely with that of Panse (36.19),[9] Bell (35.51),[7] and Davenport and Muncey (38).[18] The mean age for institutionalization for 89 males was 48.11 years and for 102 females was 48.87 years. The mean interval between onset and the first institutionalization was 10.59 years for males and 12.67 years for females.

The mean age of death of these patients was 53.04 for males and 54.11 years for females. The mean interval between onset and death was 15.78 years for males and 15.93 years for females, in comparison with Panse's figures of 13.87 years for males and 13.05 years for females[9] and Bell's of 13.72 for the 2 sexes together.[7] Suicide was an important cause of death in noninstitutionalized patients and accounted for 7.8% of deaths in males and 6.4% of deaths in females.

Inasmuch as some previous American studies have emphasized Southeastern England as the area from which the choreic ancestors of American choreics came, it is of interest to

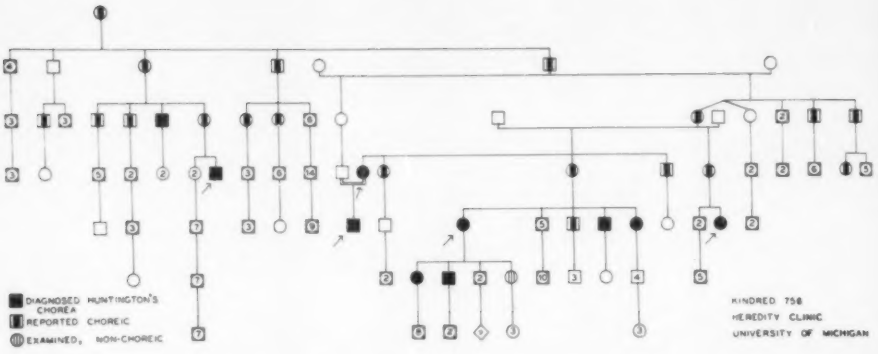

Fig. 2. Pedigree of a family with Huntington's chorea, showing a large number of cases and dominant inheritance

record the earliest known "origins" of the gene for Huntington's chorea present in the patients studied by us. Of 51 kindreds that could be traced outside of the United States, Canada, Germany, and England were the leading areas with 12, 11, and 7 kindreds, respectively. Of the American kindreds traced outside of Michigan, the largest number came from the State of New York, with 19 kindreds. Other foreign countries respresented included Poland, Ireland, Scotland, Italy, the Netherlands, Austria, Czechoslovakia, Finland, Greece, Hungary, Spain, and Yugoslavia.

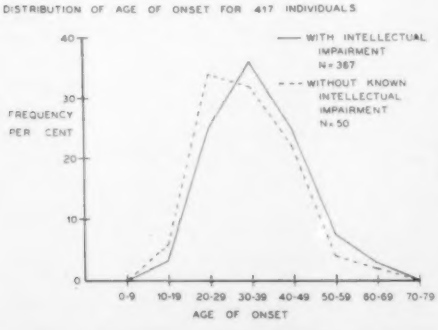

Fig. 3. Distribution of age of onset of Huntington's chorea for 417 individuals in whom emotional impairment was definitely known to be either present or absent at time of onset

CLINICAL ASPECTS

It is not the purpose of this presentation to review the major clinical manifestations of Huntington's chorea nor to discuss its pathology. The abnormal involuntary movements, emotional disturbance, and intellectual deterioration are well-known to all neurologists, as is the dominant inheritance (Fig. 2), but certain aspects of the clinical picture may be stressed. There is much individual variation in the relative order of appearance, prominence, and rate of progression for each of the 3 major manifestations. The severity and order of appearance is variable in members of separate generations, and it was not possible to confirm previous statements that age of onset, degree of motor involvement, and extent of mental deterioration all show family differences;[18] this may be true in some families and not in others. Also, we were not able to demonstrate the presence of anticipation (the appearance of the disease at an earlier age in each succeeding generation), although that, too, has been reported in the past.[21] It appears, however, that, for a given duration of Huntington's chorea, the disease is generally more severe in cases of early onset (15 to 40 years) than in those of late onset (55 to 65 years). In those patients with early onset, the emotional disturbance is often more prominent and precedes chorea and intellectual loss by months or years (Fig. 3). In 209 choreics born in 1892 or before, the mean age of onset in those with

emotional impairment was 38.62 years and, in those without known emotional impairment, it was 47.50 years. In 208 patients born after 1892, the mean age of onset in those with emotional impairment was 32.06 years and, in those without such impairment, it was 37.83 years. With older age of onset, on the other hand, choreiform movements and progressive dementia are more often the initial components and have their onset at nearly the same age (Fig. 4); the emotional disturbance is usually less prominent.

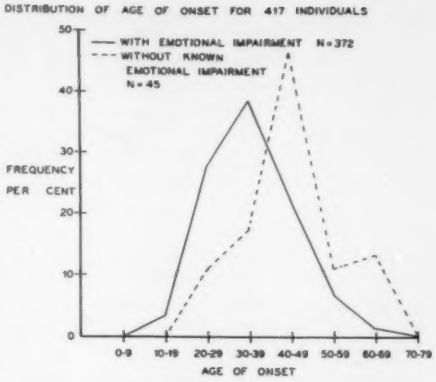

Fig. 4. Distribution of age of onset of Huntington's chorea for 417 individuals in whom intellectual impairment was definitely known to be either present or absent at time of onset

It has long been apparent to clinicians and investigators of Huntington's chorea that mental deficiency, convulsive disorders, alcoholism, abnormalities of behavior, suicide, criminal tendencies, and "insanity" occur commonly in families of patients with this disease.[10,21] Our study confirmed this, but, in addition, associated neurologic manifestations were present in many of our kindreds. These included parkinsonism, cerebellar syndromes, spastic quadriplegia, and dementia (Fig. 5). It is not known whether these are chance associations or the result of unusual manifestations of the gene for Huntington's chorea, but the former is presumed.

The diagnosis and differential diagnosis of Huntington's chorea should be mentioned. The diagnosis often is not made until many years after the onset of symptoms, even in families in which the disease is known to exist. There are many reasons for this. The patient and members of his family may, either consciously or unconsciously, fail to give the details of the family history or to mention similarity between the patient's symptoms and those of others in the family. They may give the cause of death of parents (for instance, pneumonia) but omit reference to choreic manifestations or mental disease. Huntington's chorea is relatively rare, and many physicians, even psychiatrists, fail to consider it in diagnosis; the abnormal movements, especially if mild, may be considered to be tics or "nervous" manifestations, and insufficient weight is given to mental and emo-

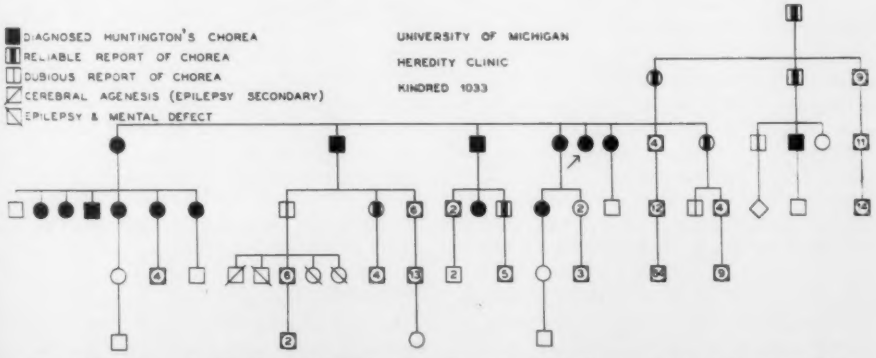

Fig. 5. Pedigree of a family with Huntington's chorea in which there were also instances of epilepsy and mental deficiency

tional changes. On the other hand, our study has shown that many other neurologic conditions especially those with hyperkinetic manifestations, have been mistakenly diagnosed as Huntington's chorea. In the younger age group, these include chorea minor, hepatolenticular degeneration, lipoid storage diseases, dystonia musculorum deformans, athetosis, choreoathetosis, and spinocerebellar syndromes, among others. The conditions incorrectly diagnosed as Huntington's chorea in the middle-aged group included familial or essential tremor, cerebellar degenerations, Parkinson's disease, conversion states, chronic alcoholism, multiple sclerosis, dementia paralytica and other forms of central nervous system syphilis, and various presenile organic mental deteriorations. The important conditions to be differentiated in the older age group include the senile and arteriosclerotic encephalopathies, the senile form of familial tremor, and so-called senile chorea. The latter differential is often difficult to make, because Huntington's chorea of late onset is often insidious in development, without associated emotional disturbances, and may progress slowly for many years. In the current study, it was necessary both to reject many kindreds including patients incorrectly diagnosed as having Huntington's chorea and to include a large number of patients with this disease whose original diagnoses have included one or more of the conditions listed above.

PREMORBID TRAITS AND PREDICTION

In a disease that is known to be inherited as a dominant trait but the manifestations of which are not apparent until late in the childbearing period, it would be most valuable to be able to predict the development of the disease, since only those who develop it will pass it on to succeeding generations. No useful differences that would aid in predicting the development of the disease in offspring of known choreics were found between nonchoreic siblings and the general population of the State of Michigan with respect to occupational, educational, or marital status. Some years ago, an attempt was made to predict the development of the disease in children of known choreics by means of electroencephalography;[22] a follow-up of this was disappointing. Our present data can in no way refute an earlier statement by Hughes[21] that potential choreics do not differ materially from their nonchoreic siblings in early temperamental traits and behavior and that there seems, as yet, to be no reliable indicator in early life of the later development of the disease.

SPORADIC CASES AND MUTATION IN HUNTINGTON'S CHOREA

As has been definitely established previously, Huntington's chorea is determined by a gene showing dominant inheritance. Mutation occurs in most well studied dominant traits in man, and evidence indicates that such mutation from the normal form of the gene to the mutant, disease-producing form takes place at a frequency of the order of 1 in 100,000 genes per generation.[23] When mutation occurs, the individual receiving the mutant gene represents a sporadic case of the disease and is able to pass it on to his offspring. Ideally, a mutation of Huntington's chorea should satisfy the following conditions: [1] the individual should have characteristic clinical features of the disease; [2] both parents should be living beyond the age of 65 years and found to be free of symptoms and signs by both clinical history and neurologic examination; [3] evidence should be present that the mutant produces affected offspring.

In the search for mutations, 36 individuals were found who had well documented, characteristic clinical findings and course for the disease but without supporting family history. Autopsies were performed on 11 of these, and pathologic findings compatible with a diagnosis of Huntington's chorea were present. Exhaustive correspondence and diligent field work uncovered only inconclusive pedigree information for 33 of these 36 patients. In most cases, a living relative could not be found. In several instances, the parent had died accidentally or from some other cause before reaching the age of 65. A "negative" family history was found in only 3 instances, but, in none of these in which the parents were reported to have been unaffected beyond the age of 65, were the parents available for clinical examination.

An instructive example of the difficulty in assuming a "negative" family history can be reported by mentioning a case of a male patient, aged 44 years, with symptoms quite typi-

cal for Huntington's chorea but whose family history, prior to our investigation, was without other instances of the disease. The parents were reported normal at the ages of 77 years (father) and 68 years (mother). The patient's wife, family physician, and the superintendent of the nearby mental institution to which the patient was committed all stated that the parents and all other relatives were normal. When, however, the family (which lives outside the State of Michigan) was visited and neurologic examinations were carried out, typical Huntington's chorea was found in 1 brother aged 41 and, in the father, there were definite although mild symptoms of the disease as evidenced by flexion and extension movements of the wrists and fingers, jerking movements of the shoulders, torsions of the trunk, and fleeting flexion movements of the lower extremities. Since the family, whose members were quite intelligent, did not recognize any abnormality in the father, his age of onset is unknown.

DISCUSSION

Our clinical observations and statistical data are in agreement in most respects with those of other large surveys of Huntington's chorea.

Huntington's chorea is an inherited progressive degenerative disorder of the central nervous system with onset in adult life. It is universally accepted that a single, dominant autosomal gene is responsible for expression of the trait.[23] The basic clinical pattern is uniform. It may be transmitted by either sex, and the 2 sexes are affected in equal numbers. The trait is transmitted directly from affected person to affected person with no break in continuity; it appears in approximately 50% of the offspring of those having the disease. No increase in central nervous system disease is apparent in nonaffected siblings.

Beadle[24] in 1945 first proposed that each gene exerts its effects by way of a single enzyme. Further experimental support for this proposition was reviewed and presented by Horowitz and Fling.[25] If derangement of a single enzyme is postulated as a basic cause for Huntington's chorea, such an enzyme would necessarily be widely distributed through the central nervous system.

The authors wish to express their appreciation to Dr. James V. Neel, Dr. Margery W. Shaw, Mrs. Estella M. Hughes, Mrs. Ruth T. Davidson, and the superintendents of the Michigan State hospitals, the Wayne County General Hospital, and the Battle Creek and Dearborn Veterans Administration hospitals for their cooperation and assistance in this study.

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Figures 3 and 4 on pages 150 and 151 should be transposed. The cutlines are in correct position.

Electroencephalographic findings and recovery from aphasia

Ronald S. Tikofsky, Ph.D., Kenneth A. Kooi, M.D., and Madison H. Thomas, M.D.

ALTHOUGH MANY AUTHORS have described abnormal electroencephalographic patterns in patients with aphasia,[1–8] the possible prognostic value of the electroencephalogram for recovery of speech has not been formally recognized. A measure to aid in estimating the ultimate prognosis of aphasic patients would be of value in planning the direction of treatment, estimating duration of treatment, and predicting the possibilities for economic and social rehabilitation of these individuals. The finding of Van Buskirk and Zarling[9] that electroencephalographic patterns are related to the course of rehabilitation in vascular hemiplegia permits speculation that progress in speech therapy might be similarly related.

As part of their neurologic study, many of the aphasic patients undergoing speech therapy at the Veterans Administration and Salt Lake City General hospitals were examined electroencephalographically. Preliminary evaluation of the electroencephalograms of these patients suggested that electroencephalographic patterns might relate to the patient's improvement in speech. From gross clinical observations, it appeared that the most fruitful electroencephalographic patterns to explore would be the background frequencies and the over-all delta incidence of each hemisphere.

PROCEDURE

A total of 33 adult aphasic patients who had received speech therapy for periods of two months to two years was divided into "no progress" and "fair to good progress" groups. Progress was determined by an examination of the therapy records compiled by the speech therapists who had worked with the patients. Patients who demonstrated definite and consistent improvement in any of the language areas found to be impaired in the initial speech examination were placed in the "fair to good progress" group.

PROGRESS IN SPEECH THERAPY RELATED TO ELECTROENCEPHALOGRAPHIC BASIC FREQUENCY

	No progress		*Fair to good progress*	
	Hemisphere		*Hemisphere*	
Dominant frequency	*Left*	*Right*	*Left*	*Right*
8.5 cps and above	3	4	11	16
Below 8.5 cps	13	11	6	1
Totals	16	15*	17	17

*Pattern on right not classifiable in 1 case

Patients who demonstrated either little or no improvement in the language areas found to be impaired in the initial speech examination were placed in the "no progress" group. Of the 16 patients who were in the "no progress" group, 14 had a diagnosis of cerebrovascular accident and 2, posttraumatic encephalopathy; of the 17 in the "fair to good progress" group, 10 had a diagnosis of cerebrosvascular accident, 6, posttraumatic encephalopathy, and 1, focal encephalitis. Average age of the patients in the "no progress" group was 56 with a range of 34 to 69 years; average age of the patients in the "fair to good progress" group was 42 with a range of 23 to 64.

All of the subjects were given electroencephalographic examinations before or early in the course of speech therapy. The electroencephalographic recordings were made on a Grass Model III D electroencephalograph, using both scalp to scalp and scalp to ear combi-

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nations; 8 electrodes were placed on each side of the head in the frontal, lower premotor, anterior temporal, midtemporal, posterior temporal, central, lateral parietal, and occipital positions.

The analysis of the electroencephalographic records was based on the frequency of cerebral patterns and their relative incidence and location. The dominant occipital frequency for each hemisphere was determined from epochs characterized by well developed rhythmic activity. This was recorded to the nearest 0.5 cps. Frequencies above 8.5 cps and below 13 cps were considered to fall within the normal alpha range.

A delta incidence score for each of the electrodes was obtained in the following manner: a score of "3" was given for a particular electrode if episodic slow wave activity within the frequency range of 0.5 to 3 cps occurred more than 66% of the time; "2" if this type of episodic activity occurred 33 to 66% of the time; and "1" if this activity occurred 33% of the time or less or if only 4- to 7-cps slow wave activity was present. The sum of the scores for all 8 electrodes for the right or left hemisphere was considered as the subject's over-all delta incidence for that hemisphere. Electroencephalograms and speech therapy records were evaluated independently.

RESULTS

The number of patients with dominant patterns above and below 8.5 cps in the 2 therapy progress groups are indicated in the table. Patterns below 8.5 cps were usual in those aphasic patients who made no significant progress during therapy. The prognosis was very poor in those patients with an abnormally slow pattern over the *right* hemisphere, as well as the left. The differences between the average basic frequencies over each hemisphere for the "no" and "fair to good" progress groups were highly significant (right hemisphere, $t = 4.2$, $p < 0.01$; left hemisphere, $t = 2.8$, $p < 0.01$). Similar "t" values were obtained when only those patients in the 2 groups with cerebral vascular accidents were compared (right hemisphere, $t = 4.1$, $p < 0.01$; left hemisphere, $t = 2.3$, $p < 0.05$).

The 2 groups of patients were also compared with regard to the degree of over-all hemispheric delta incidence. The "t's" were not significant at the 0.05 level of confidence for either hemisphere (right hemisphere, $t = 0.41$; left hemisphere, $t = 1.75$).

DISCUSSION

The results presented above suggest that the electroencephalogram may give information of predictive value relative to recovery from aphasia. The basic frequency appears to be an important prognostic index, good recovery being the rule (12 of 13 cases) with frequencies within the alpha range and rare (1 of 12 cases) with frequencies below the alpha range over both hemispheres. When the basic frequency was below 8.5 cps over the left hemisphere only, partial recovery was frequent (5 of 7 cases). Lesser delta incidence and areal spread over the left hemisphere were also correlated with good recovery from aphasia, although the relationship was not high. Thus, left hemisphere delta activity should receive only minor weight as an indication of poor prognosis, occasional patients being seen who do well in therapy even in the face of a moderate to marked delta wave hemispheric abnormality. The higher correlation between relearning speech and right hemisphere basic frequency is intriguing and suggests the possibility of an as yet undefined role for the nondominant hemisphere in recovery from aphasia.

Perhaps these findings also require a reevaluation of the functional or behavioral criteria of prognosis. It is essential to recognize that aphasia is, by definition, a symptom of brain damage. Up to the time of the present study, no measures of physiologic function of the brains of aphasics have been employed as a prognostic device. The present findings suggest that certain characteristics of the brain damage, as reflected in the electroencephalogram, are important variables that partially determine the course of recovery. It is desirable to utilize this information, in addition to evaluation of the "premorbid personality," and other qualitative means of evaluating the patient's history and test results. The electroencephalographic data do not supplant other means of predicting the success of therapy but constitute an integral part of the over-all evaluation of the patient.

SUMMARY AND CONCLUSIONS

A sample of 33 adult aphasic subjects who had received speech therapy for a period ranging from two months to two years was divided into 2 groups, those who made no progress and those who made fair to good progress in therapy. Electroencephalographic recordings for each of the subjects were made before or early in the course of the subject's therapy. Their recordings were analyzed in terms of the background frequencies for each hemisphere and delta distribution and incidence over the left and right hemispheres. The results of the statistical analyses indicated relationships between the electroencephalographic variables and recovery. Poor progress was usual when patients exhibited abnormally slow electroencephalographic patterns. A comparison of the basic frequencies of the right hemispheres differentiated the "no progress" and "fair to good progress" groups better than those of the left hemisphere, although both were highly statistically significant.

It is concluded that there is strong evidence to suggest that subjects with slow background electroencephalographic frequencies may do poorly in speech therapy, particularly if both hemispheres are involved. A left hemisphere delta focus, however, is not inconsistent with a good prognosis.

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Dynamic measurement of rigidity, strength, and tremor in Parkinson patients before and after destruction of mesial globus pallidus

David D. Webster, M.D.

THE DIFFICULTIES in quantitating the many functional and organic disturbances found in Parkinson's disease are well known.[1] Various machines have been devised to measure rigidity and tremor objectively. Schaltenbrand[2] was one of the first to describe Parkinson muscles as acting "like gum," that is, nonelastic and requiring longer time to adjust to a change of position. McKinley and Berkwitz,[3] using constant acceleration, were able to detect quantitative differences in the tone of Parkinson patients and differences in males and females. Smith and associates[4] sought to analyze tone through an energy concept, but their method was exceedingly cumbersome. Recently, Spiegel and associates[5] and Agate, Doshay, and Curtis[6] have described machines that automatically record torque as a function of angular displacement of the forearm at slow constant velocities. Tremors have usually been recorded at rest or in fixed positions using small accelerometers,[6] magnets,[7] or strain gauges.[8] The results of these tests, however, have not correlated well with surgical and medical therapies, especially when subjected to statistical analysis.[9] Our own attempts over a period of years to measure Parkinson tremor at rest with a 2-dimensional photo cell system convinced us that static measurements were largely dependent on the patient's emotional feelings and that these were apt to be influenced from moment to moment by the most subtle stimuli, such as the noise of an ink writer pen. Our present dynamic method of testing was designed to minimize these extraneous factors by measuring rigidity and tremor in the biceps and triceps muscles during passive motion at fixed velocities. In this way, the flow of proprioceptive feedback into the central nervous system is somewhat stabilized at sizeable values and a more uniform testing environment results.

METHOD

The method currently in use at the Minneapolis Veterans Administration Hospital employs a powerful yet highly sensitive turntable that reciprocates in a horizontal plane through an arc of 100° at various speeds. (Details of the turntable were presented at the eleventh Annual Conference on Electrical Techniques in Medicine and Biology, Minneapolis, November 19 to 21, 1958.)[17] The patient's forearm is rigidly coupled to the turntable by a split plaster cast. Torque about the elbow joint is recorded as a positive or negative rotational force referred to a point 12 in. from the elbow axis. These forces are plotted on both linear and logarithmic pen writers. Rigid coupling between the motor unit and plaster cast virtually eliminates turntable noise in the frequency range of 8 cps and below. At maximum sensitivity, the system will record tremors as fine

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Fig. 1. Turntable used for measuring rigidity, strength, and tremor. The split plaster cast is clamped to the reciprocating arm located in the upper part of the photo. The motor mechanism is shown below. The mobile tripod frame permits the reciprocating arm to be moved to within a few inches of the patient's shoulder while the patient is seated on a dental chair (not shown).

as 10 gm. Strength is determined by having the patient voluntarily resist the turntable motion. Torques as high as 90 foot-pounds are easily measured. The position of the forearm to the arm is recorded on a third pen. A fourth pen records the net work done by the turntable in moving the patient's forearm through each 100° cycle of passive motion. A small analogue integrator accomplishes this function by summing the product of force times distance throughout each cycle. The data are indicated as inch-pounds of work per 100° cycle. (The 100° cycle usually extends from 70 to 170° and back.)

Figure 1 is a photograph of the turntable. It is essentially a tripod on wheels, which, after positioning adjacent to the patient, is locked to the floor by cams. The patient sits on a dental chair not shown in the photograph.

RESULTS

Figure 2 is a sample of the simultaneous data written out by the 4 pens during the testing of a Parkinson patient. The logarithmic scale is used only to obtain a uniform percentile error on strength measurements over a wide range of values. The linear scale reads clockwise torques exerted by the patient against the machine as an upward deflection and counter clockwise torques as a downward deflection. A tremor of 1,500 gm. at rest is seen to modulate the force plot. The displacement plot shows the linear motion of the table versus time; 3 cycles each at speeds of 5, 10, 20, and 30° per second are shown. The fourth pen prints net work at the end of each cycle. The average work for each 3 cycles is shown just below each of the 4 speeds. Note that this work is strongly positive at from 23 to 35 inch-pounds per cycle and does not change appreciably with increasing speeds. Values of this magnitude are found in most Parkinson patients while they are awake and relaxed. Note also how the tremor fades away with increasing speed of passive motion. When tremor amplitude is plotted against the speed of passive motion, the resulting area measures the tremor as a function of the proprioceptive input.

Figure 3 illustrates a typical response of the right arm of an average Parkinson patient to what we call the "rigidity activating test." During this test, the turntable reciprocates at a constant rate of 10° per second. At the beginning of the first of 3 consecutive cycles, a flashlight is placed in the patient's free hand and he is told to follow the beam of a second flashlight held by the operator and directed onto a screen. At the end of 3 cycles, the flashlight is turned off and the patient told to relax. Originally, the activating test was designed to keep patients awake, since rigidity was found to drop to normal values during sleep. There are thus 3 distinct plateaus—sleep, wakefulness at rest, and activation.

Figure 4 illustrates how the above data are compressed into bar graphs. Bilateral tests are shown for 6 normal controls. Right arm values of rigidity appear as open bars, left arm values as solid bars. The left side of each bar is the average of 12 cycles of resting rigidity. The right side of each bar is the average of 6 to 9 cycles of activated rigidity. The individuals were selected to show the maximum and minimum limits of strength and rigidity recorded in normals thus far. Data are shown for 4 men and 2 women. There is no response to the activating test in this group. However, a striking correlation is seen between resting rigidity and muscle strength. This probably represents the basic internal frictional losses within the muscles for a cycle of movement. Normals have

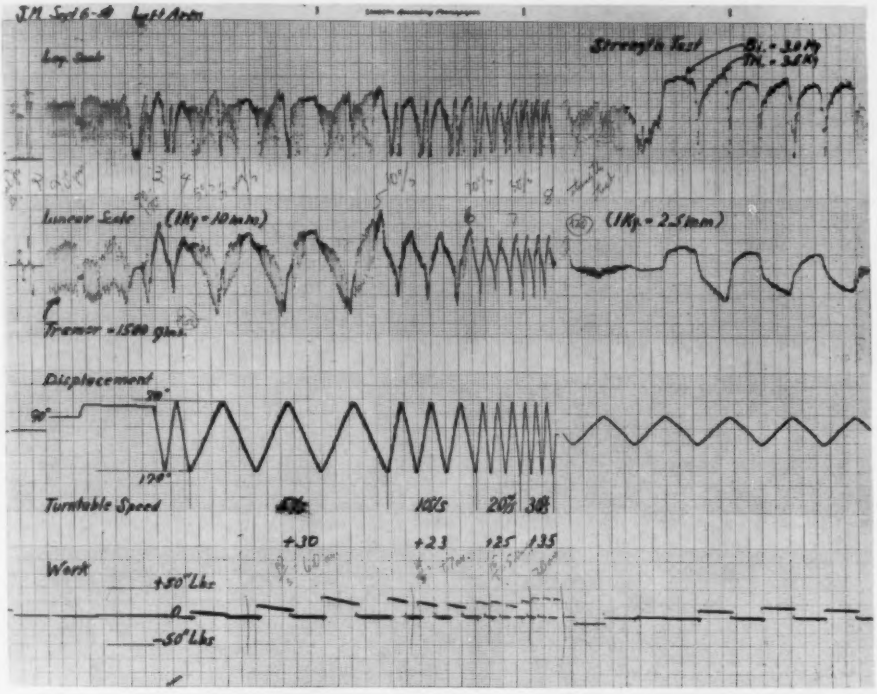

Fig. 2. Sample of the raw testing data recorded by the 4 pen writers on an average case of Parkinson's disease during resting conditions. Calibration signals are seen at the extreme left of the upper 2 pen tracings. A 1,500-gm. tremor envelope is labeled while the turntable rests at the 90° position. Turntable speeds are identified below the displacement record. The net work per cycle is read from the bottom record each time the turntable reverses at 170° displacement.

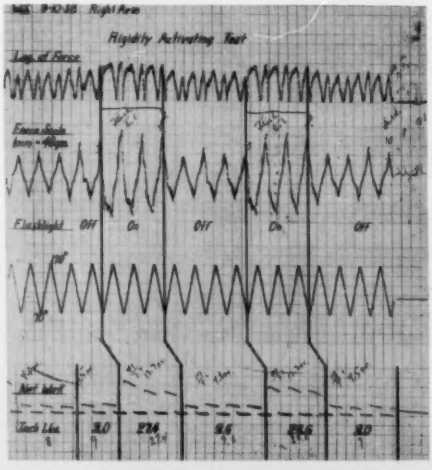

Fig. 3. Sample of the raw testing data recorded during a parkinsonian activation test. The vertical bars indicate the duration of each test. Time runs from left to right. The read-out data of the lower pen are delayed 1 cycle in the integrator. Note the instantaneous tripling of work (from 9 to 27.4 inch-pounds in the first test and from 9.6 to 26.6 in the second test) each time the activation test is run.

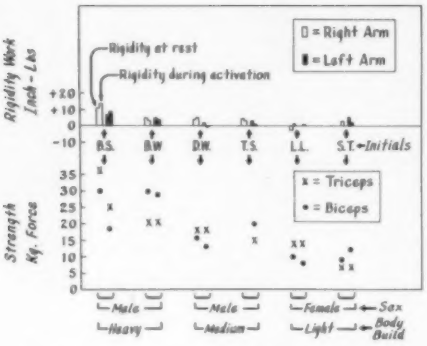

Fig. 4. Strength versus rigidity in normal controls. Data are shown on 6 normals having a wide range of strength. It is obvious that resting rigidity decreases with decreasing muscle strength.

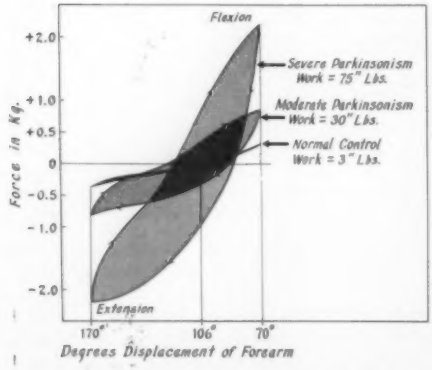

Fig. 5. Hysteresis work curves in Parkinson's disease. Work curve plots of force versus position are shown for a normal control and 2 cases of Parkinson's disease. Note that maximum forces required to move the moderately involved Parkinson arm are only double the normal control. However, the work ratio, as recorded by the integrator, is 10 times as great.

a tendency to push the turntable along in whatever direction it is turning. When this exceeds the frictional forces, a negative work is registered. This appears to be a central nervous system reflex, since negative work is abolished by very light anesthesia.

Figure 6 shows the medication response of rigidity, strength, and tremor in a moderately severe, left-sided Parkinson patient. Note the daily increase of resting and activated rigidity during the first week as he withdrew from his previous medication. Tremor is shown plotted on a logarithmic scale. High values are recorded daily in the left arm at all 4 testing speeds. There is a marked bilateral paresis while off medication. On March 20, Cogentin was started, resulting in an immediate drop in resting rigidity, an increase in strength, but little change in tremor. On March 25, Benadryl was added. A slight improvement in tremor and lessening in resting rigidity can be detected. Note that the activated rigidity of the left side is fairly constant over the entire period of testing. The degree of reduction of resting rigidity during the period of medication compared to the premedication values is significant to the .001 level.

Figure 7 is a twelve-hour graph of the previous patient's response to a single injection of intravenous hyoscine on March 17. Only the left arm is shown. The beginning values of tremor and rigidity are close to those of preceding tests. Considerably higher values develop coincident with the pain and fear of the intravenous puncture. Eight minutes after intravenous administration of 0.65 mg. of hyoscine, the tremor has vanished and rigidity is normal. At this time, the patient complained of dizziness, blurred vision, and drowsiness. His strength was reduced 50%. One hour later, the tremor was still absent but rigidity was beginning to return. Twelve hours later, rigidity and tremor were still slightly reduced. Strength had fully recovered.

Figure 8 illustrates the dramatic response of severe postencephalitic parkinsonism to electrocoagulation of the right globus pallidus. Preoperative examinations twice show marked activation of rigidity and moderate left-sided tremor; 2 postoperative examinations reveal a marked decrease in activated rigidity and a moderate decrease in tremor. A transient weakness of the left side was present four days postoperatively but not ten days later. The patient was markedly improved clinically and was kept on the same schedule of medications pre- and postoperatively. Preoperative medication probably accounts for the low values of

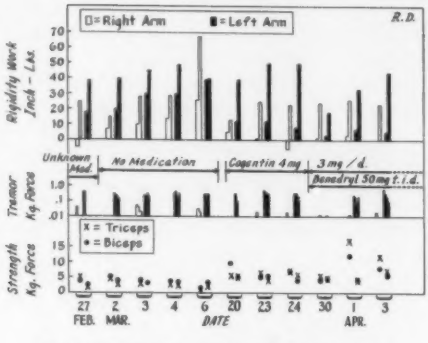

Fig. 6. Response to oral medication in moderately severe left-sided parkinsonism. Each bar graph represents the average of 10 or more rigidity readings. The left half of each bar is resting rigidity. The right half indicates the response to activation. The decrease in resting rigidity following medication is significant to the .001 level.

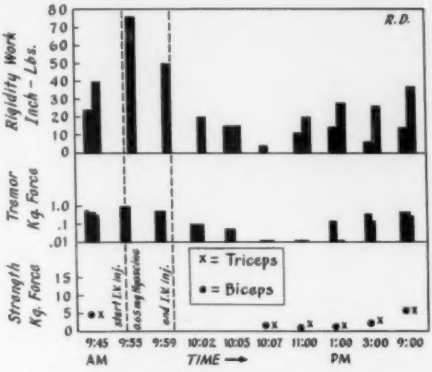

Fig. 7. Twelve-hour response to intravenous injection of 0.65 mg. of hyoscine (left arm only). Only activated rigidity is shown during the injection period due to the constant manipulation of the patient's right arm. See text.

resting rigidity and the relatively slight improvement of these values with surgery. The statistical analysis using Fisher's "t" test is shown in the table.

Figure 9 shows how a 42-year-old Parkinson patient failed to respond to variations in preoperative medication. Postoperative testing revealed mild yet highly significant reduction in both resting and activated rigidity bilaterally. This corresponded with sufficient clinical improvement to permit his return to work. The mean values shown exclude the pre- and postoperative testing while he was off medication on August 11 and 12 and October 28.

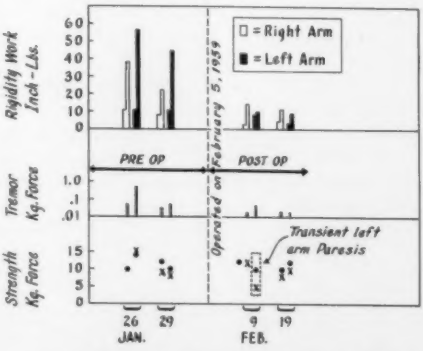

Fig. 8. Effect of electrocoagulation of right mesial globus pallidus on severe postencephalitic parkinsonism. The bar graphs have the same meaning as in previous figures. Note marked reduction in activated rigidity bilaterally after operation.

DISCUSSION

There is no question that tone is increased in Parkinson's disease. Failure to swing the arms while walking is but one example. Previous machines have evaluated increased tone as the amount of torque required to initiate motion[10] or found opposing sustained movements.[11] The data of Figure 5 show that the area of the hysteresis work curve is a more sensitive measure of rigidity. It is relatively independent of the positioning of the patient, since purely elastic forces are exactly canceled out every complete cycle and only nonelastic forces are recorded as work.

The activated rigidity that is so readily detected by integrated work is by no means a new discovery. Rapid and profound changes in rigidity have confounded all who have worked with Parkinson patients. Berkwitz[12] first measured the phenomenon but failed to identify it with parkinsonism. Activation is commonly seen in the daily activities of Par-

	LEFT SIDE		RIGHT SIDE	
	Rest	Activation	Rest	Activation
	PREOPERATIVE			
$\bar{X}_1$	10.7	50.7	9.0	30.5
$\bar{V}_1$	3.4	7.9	3.6	9.5
n_1	6	4	6	4
	POSTOPERATIVE			
$\bar{X}_2$	6.7	10.6	4.2	13.5
$\bar{V}_2$	4.8	1.4	6.9	1.9
n_2	6	5	6	4
	SIGNIFICANCE			
$\bar{X}_1 - \bar{X}_2$	4.0	40.1	3.8	27.0
t	1.7	10.0	1.5	3.5
Sig.	.045	.001	.147	.001

Table. Statistical analysis of data in Figure 8. The n_1 and n_2 values shown here were actually derived from n times 3 sets of raw data.

kinson patients when, for example, they suddenly freeze while in the midst of a voluntary act. Schwab, Chafetz, and Walker[13] have employed this as a clinical test. Rabiner and Frugh[14] described cases of sleepwalking Parkinson patients who were temporarily free of rigidity. Such a state probably represents deactivation and would appear to correspond to our findings that Parkinson rigidity disappears in natural sleep and light anesthesia.

As to the mechanism of activation, we can only speculate. It seems logical, however, that this represents an exaggerated, diffuse discharge of a synergistic system resulting in a rapid freezing and unfreezing of all muscles. Kuffler and Gerard[15] have identified the locking action of frog muscles to discharges through the small motor or gamma fibers, which produced very localized electromyographic disturbances. This may explain why some workers[10] have reported electrical silence in the presence of muscle tone. We are presently building equipment to explore these possibilities.

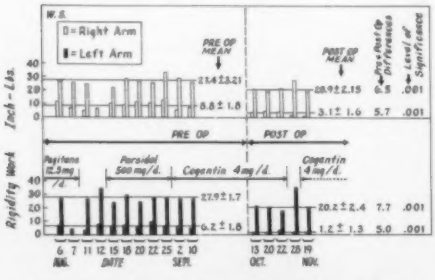

Fig. 9. Effect of electrocoagulation of left mesial globus pallidus on moderate postencephalitic parkinsonism. Rigidity bar graphs only are shown, since this patient had little tremor and strength testing showed no essential changes. The mean values of pre- and postoperative resting and activated rigidity are drawn on the graphs.

The data of Figure 7 on the twelve-hour response to hyoscine graphically illustrates one of the pitfalls in attempts to evaluate responses to medication. The response to short-acting drugs may be powerful but brief. Therefore, any testing program must be organized to test a given patient the same hour each day and at the same time after administration of his medicine. The withdrawal from medicine in Figure 6 demonstrates the difficulties with long-acting drugs reported by Agate, Doshay, and Curtis.[6] The changes may be gradual over a period of a week or longer.

The method described for recording tremor and plotting amplitude versus testing speed has great merit in our opinion, but statistical analysis will not be practical until the tremor amplitude is automatically integrated over each testing cycle.

Our present system of evaluating strength by recording only the peak of the maximum opposing force is not truly dynamic and shows rather large daily fluctuation. A much more valid strength test will result from utilizing integrated work over a restricted arc. We are presently determining the optimum parameters.

Currently, the machine is being used to measure rigidity, strength, and tremor in the pre- and postoperative evaluation of stereotactic surgery in Parkinson's disease.[16] The operated cases shown in Figures 8 and 9 are a part of this study.

SUMMARY

An apparatus has been constructed to record rotational torque versus arm position as the forearm is alternately flexed and extended through a 100° arc. Force and displacement plots are made during both active and passive motion. Torques are recorded on a logarithmic scale ranging from ± 0.02 to 90 foot-pounds.

Thus, gross tremor and cogwheeling can be detected as a modulation of the force plot. The energy required to move the forearm through a 100° arc is automatically calculated and recorded at rotational speeds ranging from 1.25 to 40° per second.

Preliminary tests show: [1] energy loss per cycle of passive motion is fairly proportional to muscle rigidity; [2] rigidity is a function of the state of consciousness; [3] simple activating procedures can be used to "precipitate" rigidity in Parkinson patients; [4] significant changes are produced by medication and brain surgery in Parkinson's disease.

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Familial hemiplegic migraine

Herbert E. Rosenbaum, M.D.

FAMILIAL HEMIPLEGIC MIGRAINE has been described as a clinical entity for almost a century. The hemiplegic type differs from the classical migraine pattern in that the aura, usually visual and of short duration in the latter type, is preceded or replaced by rather striking signs of neurologic deficit, including hemiplegia, hemisensory loss, and speech disturbances (if the dominent hemisphere is involved), as well as marked mental changes. However, in all of the numerous reports, from Liveing's[1] first description in 1873 to the more recent comprehensive study of Whitty[2] in 1953, detailed description of the underlying neurophysiologic basis has been conspicuous by its absence. Because the unpredictability of the time of occurrence and the relatively short duration of an attack make an ictal examination uncertain, it has been difficult to collect sufficient case material for a planned study. Also, unlike conventional migraine, no artificially induced syndrome has been available in the laboratory to further our knowledge of this particular malady. While the basic pathophysiology underlying migraine is not completely known, it is ordinarily assumed that the initial event is a vasoconstriction in one cerebral hemisphere, which leads to ischemia and hypoxia of the involved brain substance. This precedes the opposite phase of vasodilation, thus accounting for the prodromal and headache phases.[3] The evidences that vasodilation can produce headache are numerous and include such experiments as the use of histamine-like substances, which are known to produce dilation of the internal carotid system[4,5] and also the relief of headaches so induced by vasoconstrictors. The role of the initial vasoconstriction is not so well established, although the occasional direct observation of retinal artery spasm during a migraine aura as well as the prolongation of aura symptoms by the use of vasoconstrictors has been seen. More tangible evidence implicating vasoconstriction and cortical ischemia has been the finding of electroencephalographic changes during the aura, which are considered to be highly consistent with those produced by intentional oxygen deprivation. It is through this latter means that much of the true mechanism underlying cases of hemiplegic migraine may be learned.

Since the classical work of Hans Berger[6] appeared in 1929, showing that electrical recording of brain-wave activity was possible, much information has been accumulated to relate various states of cerebral activity to particular types of electroencephalographic patterns. While exact correlation of specific electroencephalographic patterns to brain physiology is not possible, experience has produced many meaningful observations. Among these are the following studies that bear on the relationship between headache, both nonspecific and migraine, and their electroencephalographic patterns. That many patients prone to recurrent headaches, for example, have abnormal electroencephalograms was shown by Ulett, Evans, and O'Leary[7] when they studied 1,000 consecutive subjects with headache of presumably nonorganic origin and found the incidence of clearly disordered tracings to be 9.7% in males and 20.5% in females. However, no indications could be established there relating severity of headache to expected incidence of electroencephalographic disorder. A much higher incidence of electroencephalographic abnormality was found by Dow and Whitty[8] when they reviewed 51 cases of patients with migraine headache. They had an incidence of abnormalities in over 50% of the patients in their series, which included general dysrhythmias, paroxysmal activity, and focal abnormalities. The fact that relatives of

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their migrainous subjects also had a high incidence of electroencephalographic abnormality was used by them as evidence for assuming a constitutional basis for migraine. Electroencephalograms recorded during the aura or early in the headache or with ergotamine showed no transient focal abnormalities. They did demonstrate exaggeration of the previous abnormality if one were present.

In direct contrast to this is the finding of Engel, Ferris, and Romano[9] of focal electroencephalographic abnormality in 3 migraine patients recorded only during the period of visual scotomas. These records contained irregular slow waves focal to the contralateral occipital cortex. Strauss and Selinsky[10] also present a significant incidence of electroencephalographic abnormality appearing in patients with migraine recorded during a headache and suggest that these are exaggerated by hyperventilation. Of some interest, also, are observations of Engel and associates[11] indicating that susceptible individuals can develop a typical migraine attack as a complication of decompression sickness. This usually develops within several seconds after descent and may be associated with transient occipital cortical slowing contralateral to the visual scotomas. This is in keeping with the observation of Engel, Ferris, and Romano.[9]

In such studies, a specific electroencephalographic abnormality cannot be related to migraine attacks, either in the usual or the hemiplegic manifestation. An exception has been presented by Weil[12] in a small group of headache patients in which a particular electroencephalographic abnormality, high voltage slow paroxysms, seemed to typify what he describes as "dysrhythmic migraine."

Over the past few years, I have had the opportunity to observe 5 patients presenting as diagnostic problems, in whom, after extensive neurologic investigation, the diagnosis of familial hemiplegic migraine was made. A follow-up study, ranging from several months to four years in some cases, helped to make the diagnosis more secure. Serial electroencephalograms made in 2 cases showed severe changes during the course of the illness. From these, it is possible to draw tentative conclusions as to the pathophysiology. The following are the reports of these cases.

Case 1. D.F. is an 18-year-old male with a four-year history of periodic headaches, all rather similar in nature and recurring at the rate of once or twice per year. These headaches are all characterized by a uniform type of warning, a peculiar numb feeling that begins first in the fingers of the right hand and extends up the right arm to the shoulder in a matter of twenty to thirty minutes. At the conclusion of the march of numbness, the patient notices both a suboccipital and a bifrontal headache without lateralization. The headache is steady and severe and appears to be in the scalp at first and is soon followed by a period of marked mental agitation and confusion. The headache may last from one to twenty-four hours and is frequently relieved by sleep. The mother describes the patient as being "out of his head" during the height of the headache, as well as noting that the patient had right-sided weakness. He frequently has nausea and severe vomiting late in the sequence of the headache pattern. The most serious migraine pattern occurred in October 1953, some ten months after his last episode. This was characterized by his awakening one morning and noting the onset of rather severe bifrontal and posterior headache. This particular headache gradually increased in severity and became associated with confusion, nausea, and vomiting. Shortly after onset of headache, he noted numbness and tingling of the right arm and hand and became very confused and unable to understand the meaning of questions directed toward him. Within two hours after onset of headache, moderate weakness of the right side of his body was noted and he was unable to completely express himself in a manner that could be understood.

Physical examination at the time revealed a well-developed, well-nourished young male who was obviously acutely ill. He was disoriented, very dull, and lethargic and demonstrated both a receptive and expressive type of aphasia. The general physical examination was not remarkable except for increase in body temperature and sweating on the right side of his body.

Neurologic examination revealed that the patient had marked mental confusion and a left-right disorientation. He exhibited a denial of his entire right side. Both pupils were round and regular, but the right pupil was 2 mm. larger than the left; both reacted to light and on convergence. A complete right homonymous hemianopsia by confrontation was present. A right hemiparesis, including the face and tongue, was found. Deep tendon reflexes were increased on the right side; there was an extensor response to right plantar stimulation. Sensory examination showed a total loss of stereognostic sense on the right side with a right-sided anosognosia. Pinprick and touch were appreciated on the right side but less than on the left. Coordination on the right was poor.

The laboratory examination showed a normal blood count and negative serology and urinalysis. Spinal fluid examination done twenty-four hours after onset of headache revealed 5 lymphocytes

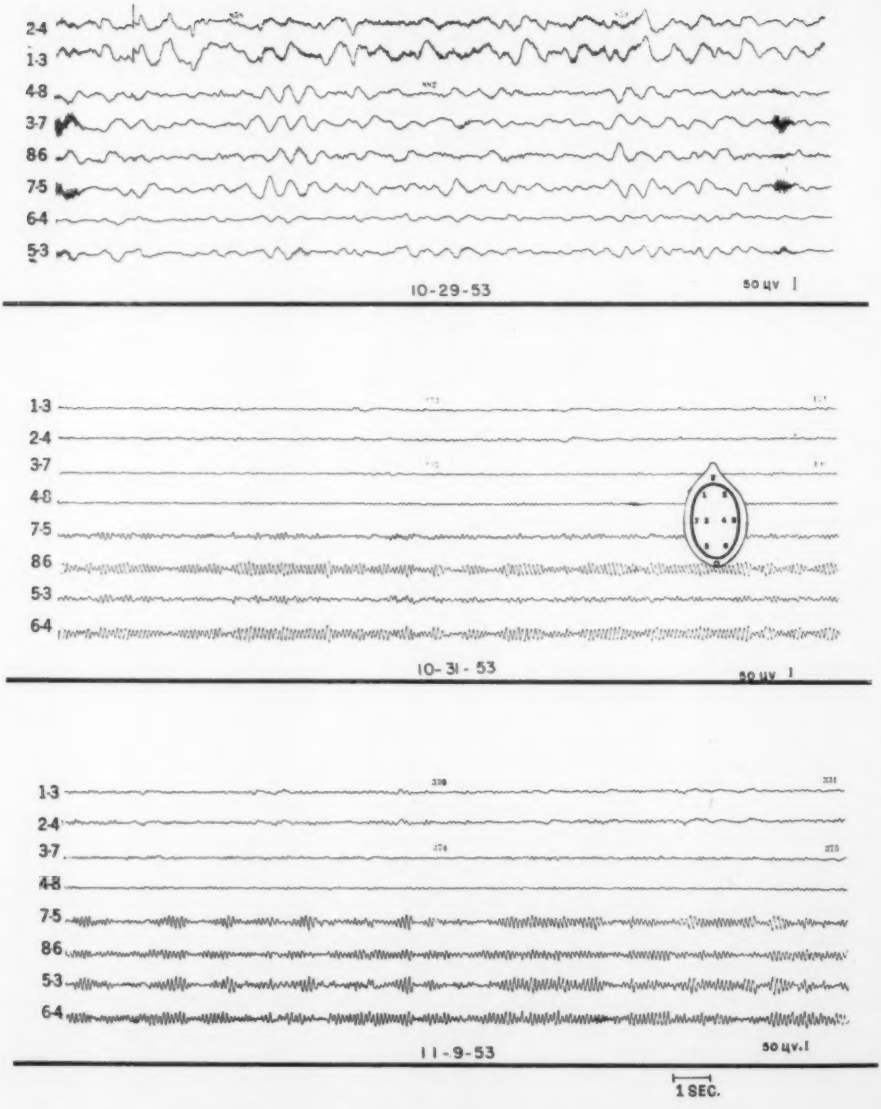

Fig. 1. Serial electroencephalograms of Case 1. The upper tracing shows the record approximately four hours after onset of the attack, at the height of neurologic signs. Note the extreme slowness together with some left-sided predominance. The center tracing was taken twenty-four hours after onset of the attack; as the headache and signs were subsiding, a definite left posterior suppression is seen. The lower tracing was recorded twelve days after the attack. At that time, the patient had been in good health for approximately ten days. A repeat record in one month was identical and considered entirely normal.

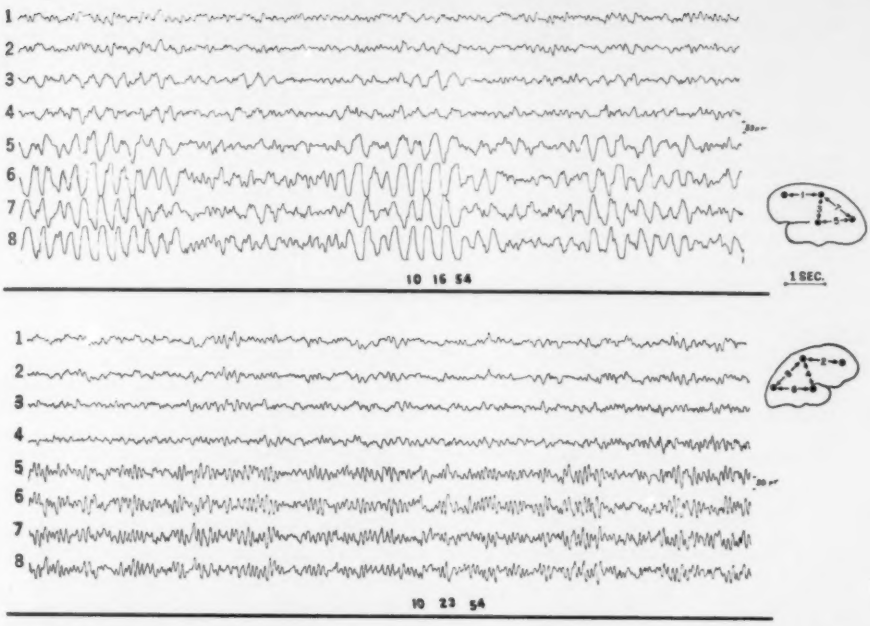

Fig. 2. Serial electroencephalograms of Case 2, showing the high voltage slow dysrhythmia twenty-four hours after onset of the attack, at which time many neurologic signs were evident, as well as a persistence of the headache. The lower tracing shows a reversion to normalcy after one week, at which time the patient was in good health.

per cubic millimeter, flat gold curve, negative serology, and 51 mg. of protein, with normal pressure and clear fluid. Skull x-rays were entirely negative. An electroencephalogram done four hours after onset of headache showed a severely slow dysrhythmia with a left sided predominence (Fig. 1).

His course was one of gradual improvement beginning approximately twenty-four hours after onset of headache; within forty-eight hours, the headache had entirely disappeared and he showed no signs of neurologic difficulty.

Family history was notable in that the mother had periodic headaches, as did 2 of the patient's siblings. None of the rest of the family has had headaches associated with neurologic signs.

Case 2. R.M., an 11-year-old school girl, was returned home from school because of what was described as peculiar behavior. History obtained from the girl after her "attack" revealed that, while at school, she had experienced numbness in both hands, more apparent on the right. This was associated with a right visual field loss. About one-half hour after onset of numbness and visual difficulty, she noted a pulsating bifrontal headache. At that time, she became confused and unable to understand language. This was soon followed by weakness of the right arm and leg.

Neurologic examination a few hours after onset of her complaints revealed right hemiparesis and partial global aphasia. The deep tendon reflexes were increased on the right side, with bilateral flexor responses to plantar stimulation. The remainder of the neurologic examination was without abnormality. Laboratory results twenty-four hours after onset of headache showed normal blood counts and urinalysis and negative serology. Her skull x-rays were entirely negative. An electroencephalogram done forty-eight hours after onset of headache revealed a marked slow dysrhythmia that was nonfocal. Her course was one of gradual improvement with complete disappearance of the headache in twenty-four hours; within forty-eight hours, her neurologic examination was entirely negative.

Past history revealed that she had had a similar episode four months before the above described attack, which was similar but less severe and of shorter duration. Family history was revealing only in the fact that a maternal uncle had periodic sick headaches associated with nausea and vomiting.

Recent communication with her family physician revealed that she has had occasional headaches during the past four years but remains in excellent physical condition.

Case 3. G.H., a 21-year-old laborer, had a history of recurrent headache patterns of six to seven years' duration. The headaches had been occurring at the frequency of 2 to 3 times a week to once every six months. His headache pattern consists of scintillating scotomas lasting for fifteen to twenty minutes, followed by a right-sided sensory march, beginning in the right hand and gradually progressing to the right arm and face, at which time he notes severe speech disturbance. This condition lasts for approximately thirty minutes, at which time he notes severe headache associated with nausea and vomiting. The headache was diffuse and would last from several hours to several days.

Examination twenty-four hours after headache revealed entirely negative general and neurologic examination. His spinal fluid was clear, under normal pressure, and without cells or chemical defects. The serology was negative. His complete blood counts and urinalysis were normal. An electroencephalogram performed between headache attacks showed no significant abnormalities. His skull x-rays were negative.

Family history revealed that his father had headaches associated with alternating numbness of both arms.

Case 4. M.C., a 17-year-old high school senior, had noted periodic sick headaches since age 6. On September 10, 1958, he noted a peculiar episode of confusion, with marked speech disturbance and inability to express himself clearly and to understand things that were said to him. This condition lasted approximately one and one-half hours and was followed by a severe generalized pounding headache and nausea, both of which disappeared in two to three hours. Two weeks later, he noted a repetition of the previous symptoms, associated with numbness and tingling of the right side of the body and a momentary period of "blindness." This lasted several minutes and again was followed by a pounding headache and nausea. The mother had noted periodic headaches for many years.

Neurologic examination between attacks was entirely unremarkable. Skull x-rays, electroencephalogram, and spinal fluid as well as routine laboratory examinations were all negative.

Case 5. M.W., a 22-year-old female college graduate student, was well except for occasional headaches until November 10, 1958, at which time she noted a gradual onset of numbness of the right side of her face and body associated with marked speech difficulty, all of which lasted approximately one-half hour and was followed by a severe left sided headache that remained for several hours. Following this episode, she was given a rather complete neurologic examination, including electroencephalogram, skull x-rays, and lumbar puncture, all of which were reported as being negative. She was then well until ten days later, when she was awakened by a tingling sensation in her left face and neck, which soon spread to her left arm, together with a numb sensation lasting fifteen minutes. No speech disturbance was noted; however, a right-sided headache followed and lasted for three to four hours. When examined the following day, she was neurologically negative and an electroencephalogram obtained immediately after the clinical examination showed no abnormalities. Her mother was said to have had periodic sick headaches with no neurologic phenomena.

DISCUSSION

These cases, as well as similar ones reported in the literature, present a diagnostic challenge. When confronted with the sudden onset of serious neurologic symptoms and rapidly progressing signs, one must think of many different pathologic states, including the differential diagnosis among infectious processes, vascular disease of all types, and neoplasm. In the above cases, as well as in the case material in the literature, there are several noteworthy facts. This particular illness usually has its onset in young adult life, and the majority of cases have occurred in persons under the age of 30. The sex distribution is not remarkable; however, a family history of migraine seems to occur in most instances and is helpful if present. These patients are entirely well up to an attack and recover completely; this is very significant. The clinical signs frequently alternate from side to side from attack to attack. And lastly, the clinical types seem to fall into 2 somewhat dissimilar groups. In 1, as in Case 1, the sequence of events is strikingly similar to classical migraines, having an aura followed by headache, except that the usual visual phenomena ordinarily constituting the aura are replaced or become associated with other neurologic signs. As the headache appears, the neurologic signs wane and disappear. In the second type, the headache may precede the "aura" and the neurologic signs are usually prolonged, lasting for several hours or days. In consideration of the possible causes of sudden hemiplegia in a young person, vascular malformations, such as aneurysms and arteriovenous anomalies, have a high incidence. While these must be thought of, the absence

of any evidence of bleeding and the relatively rapid return to well-being is certainly against these diseases as causing the episodes in our series. Angioma and other tumors do occasionally produce intermittent and recurrent symptoms, but, here again, the fact that these patients resume normal health and have been followed for a significant period of time thereafter is much against this possible etiology. No sign of infection was present in any of the patients, either by clinical examination or laboratory results of blood, urine, or spinal fluid studies.

If we can logically rule out all of the so-called "structural" causes for this clinical picture, then the various "functional" forms of disease must be considered. Because of the severity of the symptoms in hemiplegic migraine, it must be assumed that there is a marked disturbance in the underlying cortical activity. In attempts to elucidate the basis for this disturbance, 3 major types of physiologic changes have been considered. The paroxysmal nature, often with explosive onset, is somewhat analogous to the epilepsies. The incidence of migraine in patients with convulsive disorders is somewhat higher than in the population as a whole, but the association is not striking. It should be noted that none of the patients reported had any history of seizures and all had "normal" electroencephalograms between headaches. A second possible mode of producing severe temporary cerebral dysfunction is arterial spasm as it relates to the current concept of the pathogenesis of the ordinary migraine syndrome. In respect to this, it is of interest to note that Darrow and Graf[13] induced abnormal high voltage electroencephalographic activity in cats by producing cerebral vasoconstriction. These brain-wave patterns were not unlike those seen in Cases 1 and 2 early in the attack. What initiates the spasm is totally unknown. However, if it is assumed that spasm alone is responsible for the neurologic deficit, it seems unlikely that an ischemic process could last for a matter of hours without leaving in its wake some permanent residual. A more tenable theory seems to be that the spasm trips off a mechanism whereby cerebral edema occurs. This may well be analogous to "angioneurotic edema of the brain," suggested first by Osler.[14] The findings of apparent focal suppression over the involved hemisphere toward the end of the attack, as seen in the second electroencephalogram of Case 1, may well be a reflection of localized edema. Whether oligodendrogliocytes are capable of reacting to spasm in this fashion or whether it is an allergic response as proposed by Kennedy[15,16] is yet to be proved. Certainly, the concept of a reversible focal edema of the brain giving rise to prolonged signs and symptoms that clear completely is more logical and compatible with the electroencephalographic findings than is simple ischemia secondary to vasospasm. Another possible mechanism was mentioned by Milner,[17] who drew an analogy between the scotomas of migrane and the spreading depression of Leao.[18] While this could explain the simple patterns of hemiplegic migraine, as in those cases that seem closely related to the ordinary migraine syndrome, it seems unlikely that any process developing rapidly could in itself explain the more prolonged effects seen in 4 of our cases.

Based on the material presented, especially serial electroencephalographic changes, a possible mechanism underlying some cases of familial hemiplegic migraine is proposed. First of all, a genetic susceptibility to periodic cerebrovascular spasm. Secondly, as a response to this, the brain reacts by focal edema formation, which may persist for an indeterminate length of time and then resolve completely. What determines the initiation of the vasospasm and the subsequent edema still remains a mystery.

SUMMARY

A total of 5 cases of familial hemiplegic migraine are reported, which present 2 distinct types of clinical pictures. The first is very similar to the ordinary migraine syndrome except that the more common visual aura is replaced by more serious signs of neurologic deficit, such as hemiplegia, hemisensory loss, and aphasia. The course otherwise is identical. The second type differs in that the headache may precede the aura and the neurologic signs are usually prolonged, lasting several hours or days. Serial electroencephalograms taken during the course of this disease lend support to the view that there is an initial vasoconstriction followed by focal edema of the brain and

that this persists for a prolonged period. The disappearance of the edema would then be correlated with disappearance of serious neurologic signs and account for the absence of any permanent residual.

The author wishes to express his sincere appreciation to Dr. James L. O'Leary for his support and ideas during the course of this study.

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Permeability of cerebral blood vessels in experimental allergic encephalomyelitis studied by radioactive iodinated bovine albumin

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THE PURPOSE of these experiments was to study vascular permeability in the nervous system during the development of experimental allergic encephalomyelitis (EAE) and the temporal and spatial relationship of any changes in permeability to the histologic lesions of this disease. This information might be expected to shed light upon one aspect of the pathogenesis of this disease, namely the site of the primary lesion, which at present is not known. Should it be in the wall of the vessels, the vascular permeability might be increased before other signs of inflammation can be seen; should it be in the surrounding parenchyma, the increase in permeability could appear simultaneously with—or perhaps slightly later than—the inflammatory reaction around the vessel wall.

Barlow[2] has investigated cerebral vascular permeability in EAE, using trypan blue, and found increased permeability in regions with perivascular infiltration but not in those with perivascular cuffing. We have studied the permeability with iodinated radioactive bovine albumin, employing an autoradiographic method for its detection. This method gives a more precise localization than trypan blue and a greater intensity of staining. In addition, we can expect that study of the changes of protein permeability may be more relevant to the problem of pathogenesis of EAE, which is considered to be a manifestation of a hypersensitive reaction.

MATERIAL AND METHOD

Male and female guinea pigs of mixed breed, weighing 500 to 1,000 gm., were used for these experiments. To produce the EAE, an emulsion of equal parts of a brain suspension and adjuvant was injected intracutaneously into the anterior cervical region or abdominal wall. This suspension contained 10% fresh sterile human white matter in distilled water with 0.5% phenol. The adjuvant was a 4:1 mixture of Bayol and Falba, containing in each cubic centimeter 15 mg. of dried and heat-killed BCG; 5 spots were injected, each with 0.1 cc. of the emulsion. Thus, each animal received 20 mg. of fresh brain and 3.75 mg. of dried tubercle bacilli. From previous experiments, we knew that this emulsion would produce the histologic lesions of EAE in 98 to 100% of the guinea pigs. Starting from the sixth day after the injection, the animals were inspected twice daily for clinical signs of the disease. Paralysis of 1 limb or the inability of the animal to maintain equilibrium was accepted as diagnostic for the disease.

The permeability of the cerebral blood vessels was studied with radioactive iodinated bovine albumin. The technic used was a modification of that previously described.[1] It consists of 3 main steps: [1] the injection of iodinated albumin; [2] the washing out of blood from the cerebral blood vessels with dextran followed by saline; and [3] the preparation of autoradiographs.

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1] Under light ether anesthesia, the skin of the anterior cervical region was opened with a slit above 1 of the jugular veins. Using a 5-cc. Luer-Lok syringe, provided with a 27-gauge needle, 2 to 3 cc. of a 2% solution of iodinated bovine albumin was injected into the jugular veins. The amount of albumin injected was calculated to correspond with 330 μc. in groups 1, 2, and 3 and 250 μc. in groups 4 and 5. The slit was closed with a few stitches and the animal laid in a cage with food and water. This procedure is a very minor operation. The total time of anesthesia never exceeded five to eight minutes, and none of the animals showed any untoward reaction.

2] Six hours after injection, the guinea pigs were anesthetized with ether. The abdomen was opened and the inferior vena cava or the portal vein cannulated with an 18-gauge, 1½-in. long needle connected to an infusion set. The bottle containing 5% dextran was placed 80 cm. above the animal. The jugular veins were now exposed, clamped, and cut distally (on the head side) from the clamp. At the same time, the infusion was started. By regulating the bleeding through the jugular vein and the flow of the infusion, care was taken to avoid sudden loss of circulating volume. Thereby, the animals were maintained in life for as long as twenty minutes after the opening of the jugular veins. At the end of such a substitution transfusion, the failing heart was pumping nearly pure dextran solution slightly tinged by blood. When the heart beat became imperceptible, the chest was opened. The descending aorta and vena cava were clamped. The perfusion needle was removed from the vein and thrust into the left ventricle of the heart, saline was gravitated, and the brain was perfused. For each animal, 30 to 50 cc. saline was used. At the end of this procedure, the saline pouring from the jugular vein was colorless. The saline in the perfusion system was followed by 10% formalin in saline or 10% formalin with 30% ethanol in distilled water, thus fixing the brain in situ. Following fixation, the brain was removed from the skull and placed for twelve hours in 10% formalin. Then the brain was cut into sections 3 mm. thick and examined grossly.

3] Sections for autoradiograph were prepared from these slices. Frozen sections 25 or 50 μ thick were cut, mounted immediately on microscopic slides, and dried in air. In the darkroom, the sections were covered with strips of Kodak No-Screen x-ray films or with Kodak No-Screen autoradiographic plates. The film and slides were fastened tightly together with rubber bands and several turns of black paper. Attention was paid to avoiding the sliding of the film on the section. The time between the death of the animals and beginning of the exposure (apposition of film and section) never exceeded sixteen hours. The exposure time was exactly seventy-two hours. After this time, the films were developed for five minutes in Microdol 1:20, washed in tap water, fixed in Kodak acid fixer, washed again in tap water, and dried in air.

After the exposure of the autoradiographs, the histologic sections were stained with cresyl violet; 9 or more sections and autoradiographs were prepared from the brain of each animal.

RESULTS

We investigated the localization of the labeled bovine albumin in the brain of normal guinea pigs and in the brains of guinea pigs in different stages of the development of EAE. We performed the experiments using a total of 107 animals divided into 5 groups.

Group 1. The outlined procedures were done on 5 normal guinea pigs (60, 61, 62, 63, and 392), with the exception that they were not injected with brain emulsion, and thus they served as controls. When the brain was unperfused at all, the autoradiograph revealed focal points of intense radioactivity corresponding to the vessels in the section (animal 392, Fig. 1). Intervening tissue was only slightly radioactive, particularly in the gray matter. This was probably due to a small amount of radioactive blood in the capillary network. When the brain was perfused with saline without previous hemodilution, the autoradiograph revealed that moderate radioactivity still remained in some of the blood vessels, presumably due to traces of radioactive blood not washed out by saline (animal 63, Fig. 2). But when the perfusion with saline followed hemodilution with dextran, the blood vessels did not contain any appreciable amount of radioactivity, with the exception of the choroid plexus and hypothalamus, which were slightly

radioactive. The actual autoradiograph shows a hardly perceptible darkening over the whole section, but it was not possible to show this in a print (animal 61, Fig. 3).

In some of the animals subjected to exchange perfusion, the meninges and walls of the ventricles contained traces of radioactivity. However, there were never any patchy areas of radioactivity in the nervous tissue or around the blood vessels.

Group 2. Brain and adjuvant were injected into 14 guinea pigs; 3 animals (87, 88, and 89) were sacrificed four days after this injection and another 3 (90, 91, and 92) at eight days. The autoradiographs of these animals did not differ from those of the normal ones, and no lesions were seen in the sections of the central nervous system.

The remaining 8 animals developed clinical signs of EAE eleven to seventeen days after the injection. Of these animals, 4 (96, 97, 98, and 99) were injected with radioactive albumin on the day they became paralyzed (fourteen, fifteen, fifteen, and seventeen days after injection), and autoradiographs of their brains were prepared. Only histologic sections were made from the brains of the 4 remaining animals. All 8 animals had lesions characteristic of EAE in their central nervous systems, consisting of meningeal and perivascular inflammatory reaction. The autoradiographs will be discussed below.

Group 3. Brain and adjuvant were injected into 8 guinea pigs. On the day 3 animals of this group (145, 146, and 147) became paralyzed, the other 5 nonparalyzed animals, (130, 131, 132, 133, and 134) also were sacrificed and autoradiographs were prepared of their brains. This was done to obtain information about the autoradiographic changes in the brains of animals that had lesions and yet did not develop paralysis. The autoradiographs will be discussed below.

Groups 4 and 5. Brain emulsion was injected into 2 groups of 40 animals each to reaffirm the preceding findings and to find out what changes occurred in the cerebral permeability of chronic animals. Of these animals, 6 (352, 376, 377, 378, 389, and 390) were injected with radioactive albumin on the day they became paralyzed. Another 15 were injected with radioactive albumin at intervals ranging from one to twenty-four days after onset of paralysis (see table).

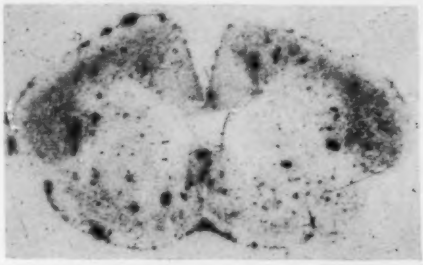

Fig. 1. Autoradiograph of a section of a brain of a guinea pig that had been injected with I^{131}-labeled albumin but not subsequently perfused. (Animal 392)

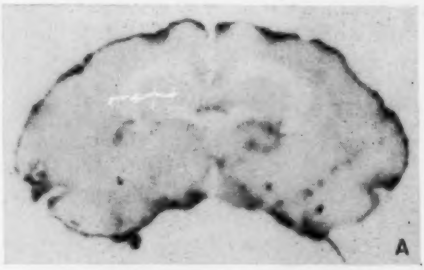

Fig. 2. Autoradiograph similar to that in Figure 1, but with saline perfusion

Fig. 3. Autoradiograph similar to that in Figure 1, after hemodilution with dextran solution followed by saline perfusion. (Animal 61)

The results of these experiments may conveniently be discussed together. The autoradiographs of the brains of animals in the acute

Days after paralysis	Animal number	Days after paralysis	Animal number
1	369, 382, 383	8	365
3	358	10	366
4	360	12	351, 359
5	350, 364	16	371
6	370	24	367
7	379		

stage of EAE grossly differed from those of normal animals and were characterized by diffuse and focal radioactivity (animal 98, Fig. 4B). A diffuse background activity produced uniform and slight darkening over the whole section. More intense darkening was present in the cortex. It was more pronounced under the pia and decreased toward the deeper layers. When numerous blood vessels over a large area were severely involved, the darkening extended from the cortex to the ventricle. In regions of gray or white matter containing many inflamed blood vessels, a diffuse moderate darkening was present in addition to patches of intense radioactivity which corresponded to the vascular lesions. The meninges, the choroid plexus, and the hypothalamus showed intense diffuse radioactivity in all animals with EAE, irrespective of the absence or presence of inflammation in these regions.

The focal accumulation of radioactivity corresponded to the blood vessels with inflammatory reaction, but no correlation was observed between the intensity of inflammation and the autoradiographic picture. Almost all blood vessels showing any inflammatory reaction corresponded to a small dark spot revealing high concentration of I^{131}. Darkened areas around neighboring blood vessels often merged together. In other instances, single blood vessels corresponded to larger areas of moderately increased radioactivity.

However, many of the autoradiographs from

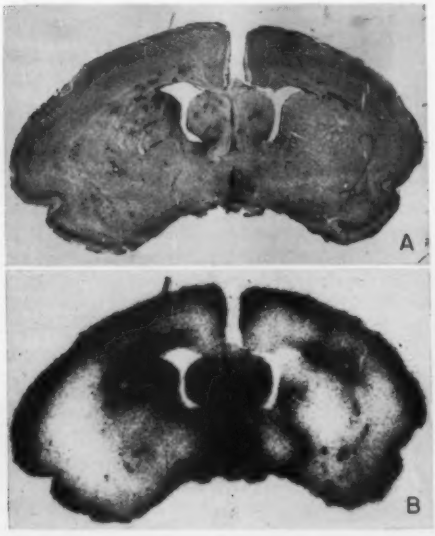

Fig. 4. [A] Nissl stained section of the brain of an animal in the acute stage of EAE. (Animal 98). [B] Autoradiograph corresponding to A. (From Marian W. Kies and Ellsworth C. Alvord, *Allergic Encephalomyelitis*, 1959, courtesy of Charles C Thomas, Springfield, Ill.)

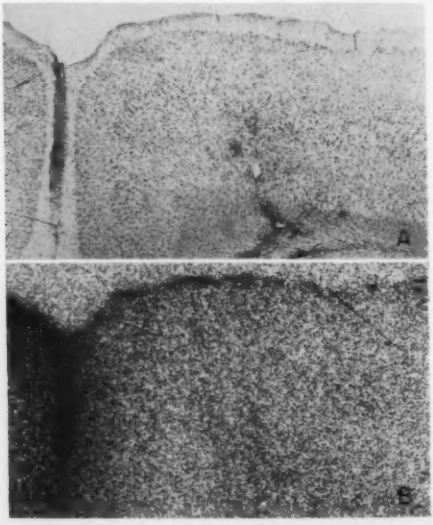

Fig. 5. [A] Section of the brain of a guinea pig in the acute stage of EAE. (Animal 97). [B] Autoradiograph of section in A. Note that there is no darkening of the area corresponding to the inflamed vessels. (From Marian W. Kies and Ellsworth C. Alvord, *Allergic Encephalomyelitis*, 1959, courtesy of Charles C Thomas, Springfield, Ill.)

acute animals also showed blood vessels with marked inflammation not surrounded by radioactivity (animal 97, Fig. 5B). Furthermore, many blood vessels corresponded to a definite spot of heavily concentrated I^{131} but showed no pathologic changes in either their walls or the surrounding parenchyma (animal 146, Fig. 6B). Particular attention was paid to the content of such blood vessels, but their lumina were always found free of blood cells, precipitated protein, and thrombi. In animals 98, 99, and 147, only 1 or 2 cerebral vessels showed this change. However, it was common in animals 145 and 146. In animal 145, the uniform darkening of the whole autoradiograph was especially prominent, particularly the portion corresponding to the cortex. Superimposed upon this, most of the arterioles and/or venules (but not capillaries) gave a focal darkening of the autoradiograph as well, although they showed no inflammation microscopically.

In general, the vessels showing increased permeability without signs of inflammation were located in the basal ganglia, but occasional examples could also be found in the cortex and brain stem. Only arterioles or venules appeared to show this change. However, once the inflammation had progressed to the stage of perivascular cuffing, the type of blood vessel affected could no longer be ascertained with confidence. Despite the increase in permeability, edema was not observed.

In addition, in certain places, the tissue along the ependymal nests between the hippocampus and the white matter of the convexity of the hemisphere was intensely radioactive without showing inflammatory changes (Fig. 6A and B).

In all animals examined later than the first day after onset of paralysis, inflammatory changes were widespread. However, the increase in permeability was very much reduced, so that the autoradiographs (animal 382, Fig. 7A and B) closely resembled those of properly perfused control animals, with the exception of a very slight darkening roughly corresponding to the areas of most intense cellular reaction.

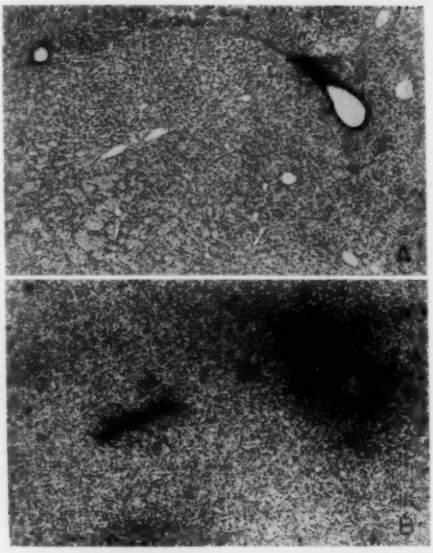

Fig. 6. [A] Section of the brain of a guinea pig in the acute stage of EAE. (Animal 146). [B] Autoradiograph of section in A. Note that some vessels without obvious inflammatory change show a marked accumulation of radioactivity. (From Marian W. Kies and Ellsworth C. Alvord, *Allergic Encephalomyelitis*, 1959, courtesy of Charles C Thomas, Springfield, Ill.)

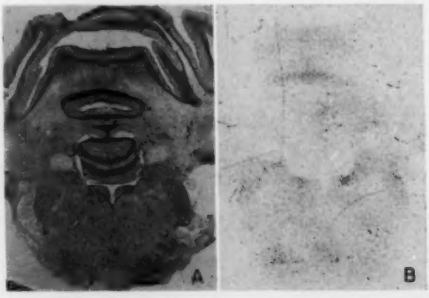

Fig. 7. [A] Section of the brain of a guinea pig in a chronic stage of EAE, made the day after onset of paralysis. (Animal 382). [B] Autoradiograph corresponding to section in A

DISCUSSION

In the following interpretation of our results, we assume that the radioactive iodine re-

mained attached to the albumin from the time of injection until the preparation of autoradiographs. This seems to be permissible, since the iodine-protein link is known to be very stable.

These conclusions can be drawn from our findings:

1] The inflammatory process of EAE is accompanied by an intense increase of vascular permeability to protein molecules. This was evident by radioactivity in all regions that contained numerous blood vessels surrounded by inflammatory cells. The radioactivity of the superficial cortical and subependymal layers and the slight diffuse radioactivity of the whole section can be explained by a likely assumption that some radioactive ablumin leaked into the cerebrospinal fluid. It is known that the brain substance becomes intensely radioactive if iodinated bovine albumin is injected into the subarachnoid space.[3] In the subependymal layer, intense radioactivity was observed in the regions in which the lateral ventricle formed narrow slits lateral to the hippocampus. Possibly, the circulation of the cerebrospinal fluid is slower in these regions, so that penetration of cerebrospinal fluid into brain tissue is more likely to occur. It could also be suggested that, in these regions, the nervous parenchyma itself has slightly different physicochemical properties that favor penetration of the protein into it. In this connection, it is noteworthy that the plaques of multiple sclerosis are most often found in regions that may be considered homologous to those in which the radioactivity in the subependymal tissue was particularly intense.

2] In many instances, we have seen that the blood vessels that corresponded to discrete spots of radioactivity did not show any perivascular accumulation of inflammatory cells or alterations in their walls nor were there any parenchymal changes around them. Since no blood was present in these vessels, we must assume that the radioactivity was originating from material either in the blood vessel wall itself or outside the vessel in the parenchyma, but we could not answer this latter question on our material due to poor resolution of autoradiographs on x-ray films. We feel that there could be 2 possible interpretations of these findings. First, we can think that these sites would have progressed to the typical inflammatory lesions of EAE had the animals been allowed to live. If this assumption is valid, these findings would indicate the presence of a vascular lesion before the appearance of cellular exudate or microglial perivascular reaction. Thus, they would support the concept that the lesions of the vessel wall may be one of the earliest phenomena in a chain of events leading finally to the full-blown pathologic picture of EAE. Second, it is possible that radioactivity at the site of blood vessels without inflammatory changes is caused by the spread of radioactive cerebrospinal fluid from the subarachnoid space along the perivascular spaces into the depth of the tissue. That such spread actually occurs has been shown by Lee and Olszewski,[3] who injected iodinated radioactive albumin into the subarachnoid space of normal rabbits and observed radioactivity not only along the superficial subpial vessels but also in association with deep vessels of the basal ganglia. It is perhaps significant that we have never observed blood vessels associated with radioactivity but without inflammation unless there was, simultaneously, an intense inflammatory reaction in other parts of the brain, as could be expected if the first explanation were correct.

3] The permeability changes associated with an acute phase of EAE lasted only a comparatively short time, since the radioactivity was much diminished the day after onset of paralysis and was absent at any later stages. This observation can explain the occurrence in the brains of acute animals of vessels that showed the typical inflammatory lesions of EAE but no permeability changes. These vessels may have passed the acute stage of inflammation at a time when the animal did not show clinical signs of disease.

We may mention in this connection an observation made by Lee and Olszewski[4] on the permeability of cerebral blood vessels in "spontaneous encephalitis of rabbits." Neither granulomatous nor perivascular inflammatory reactions were accompanied by an increased permeability to iodinated albumin. Thus, an inflammatory reaction is not necessarily associated with detectable permeability changes. This finding seems to be of considerable significance, since it indicates that lesions which

are comparable histologically may be associated with quite different submicroscopic alterations and correspondingly different functional changes.

SUMMARY

1. Permeability of the cerebral blood vessels in experimental allergic encephalomyelitis was studied.

2. Iodinated radioactive bovine albumin and the autoradiographic method were used to assess the changes of permeability.

3. Under normal conditions, the cerebral blood vessels are impermeable to the molecules of the albumin with the exception of the choroid plexus and the hypothalamus. Other regions, such as area postrema, were not studied.

4. In the initial stage of experimental allergic encephalomyelitis, the inflamed blood vessels become permeable to albumin.

5. In chronic animals, blood vessels with signs of inflammatory changes do not show increased permeability.

6. In acute animals, certain blood vessels with signs of inflammatory changes may not show increased permeability.

7. In many instances in acute animals, increased permeability was observed around blood vessels without any signs of inflammation.

8. These last findings were interpreted to indicate that either [1] the primary lesion of the vessel wall may be one of the earliest phenomena leading to the full picture of EAE or [2] radioactive cerebrospinal fluid alone can penetrate the normal blood vessels deep into the brain tissue.

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Effects of radio-frequency energy on primate cerebral activity

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and Shirley A. Lewis, R.N.

FOR EIGHTY-FIVE YEARS,[1] the primate brain has been extensively studied by means of electrical stimulation. In the laboratory, the various methods of electrical exploration have evoked responses related to the mechanisms of movement,[2] sensation,[3] and autonomic function.[4] Similar methods applied to the human brain for diagnostic purposes have evoked changes in speech, perception, and memory, as well as the somewhat less complex effects observed in laboratory primates. Actually, the technics of electrical exploration have yielded a rich harvest of data on function. Certainly, as Walshe[5] says of surface stimulation, "There are no signs that this topographical exercise evokes less enthusiasm now than at any time in this long period." Furthermore, the older methods of surface stimulation have been supplemented by the more recent developments of implantation devices that permit exploration of deep-lying nuclei, such as basal ganglia and reticular systems.[6] While these newer methods give access to different parts of the primate brain, they do not provide for a great variety in the electrical energies that can be applied. Indeed, as in the past, contemporary technics of electrical exploration employ only a relatively small fraction of the large electromagnetic spectrum.

Theoretically, electrical energy in the ultrahigh frequency and microwave ranges could be used to stimulate the nervous system. Actually, the biologic effects of these frequencies, which include the radio and radar zones, have been extensively investigated. D'Arsonval[7] pioneered in such experiments, and his research led to the development of diathermy. In keeping with this early development, most subsequent investigations end with the conclusion that radio frequencies simply heat living tissues, including those of the nervous system. According to these reports, such energy causes a thermal effect. Hartman[8] says, "It is generally agreed that these effects are due largely to local or general hyperthermia in tissues." Boysen's[9] findings are consistent with this thesis. Using a frequency of 358 mc., he exposed the "whole bodies" of rabbits. Many animals died, and, subsequently, degenerative changes were noted in cortex, basal ganglia, pons, and medulla. As in Boysen's work, most investigations have been concerned with whole body exposure of small fur-bearing animals. In a clinical study, Barron and Baroff[10] reported that frequencies from 400 to 900 mc. had little effect on human beings whose whole bodies were exposed to the radiation. Similarly, Sinisi[11] noted that human beings fully exposed to high frequency radar did not show electroencephalographic changes. Indeed, most previous laboratory investigations conclude that energy in the radio and radar ranges causes heating, while relevant clinical studies indicate that it has little or no effect on human beings. Yet, for the most part, these reports do not describe effects of frequencies in the range between 1 and 400 mc., nor is there any description of exposure of the head designed for cerebral stimulation.

The effects described here were observed during exposure of the monkey's head to 388 mc.

MATERIALS AND METHODS

The essential materials of this investigation consisted of [1] 21 young Macaca monkeys in

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good health; [2] 2 primate chairs; [3] 2 copper mesh cylinders (resonant cavities); [4] 2 quarter-wave-length probes, 1 located concentrically in each of the cavities; and [5] a standard ground-to-air radio transmitter (Collins T17A GR), which is a 100-watt communicator operating in the range of 225 to 399.9 mc. per second. This was made available through the kindness of the Naval Research Laboratory. It has since been replaced by a Stewart-Warner T 282D/GR loaned through the generosity of the Rome Air Force Base.

These materials were arranged so that each monkey sat in a primate chair with a resonant cavity (copper mesh cylinder) over its head. The top platform of the chair was carefully screened with a rectangle of copper mesh, which was soldered to the lower edges of the cylinder. Each animal's neck was insulated in order to prevent burns and yet permit movement within a hole in the copper rectangle. The hole was small enough so as to prevent significant escape of energy at this frequency. Thus, the head protruded within the copper cylinder, which extended 80 cm. upwards and 30 cm. outwards from its position. Its location was central in the base of the cylinder, formed by part of the rectangle, while the quarter-wave-length probe was centrally located in the roof of the cylinder. In this ar-

Fig. 1. The basic experimental assembly. This consists of 2 primate chairs, each of which is superimposed by a copper mesh resonant cavity. A quarter-wave antenna can be seen at the top of the cavity, close to where it connects with the cable that passes between the cavity and the transmitter.

rangement, the wave from the transmitter passed from the probe through the air in the cylinder to the animal's head, which could absorb the radiation like another antenna. Yet there was no direct connection between any current-carrying device and the animal.

Actually, the monkey's head was positioned in 1 of 2 ways. At first, it was relatively high in the cavity. In this high position, the animal had complete freedom of head and neck movement. Then, the ring of insulation described above was at the base of the neck. In the second position, the occiput rested against the posterior lip of the cervical collar and the insulating ring came close to the mandible in front. In this low postion, the neck was extended and lateral movement of the head on the neck was restricted. Then, a line drawn between the external auditory meatus and lateral aspect of the orbit intersected the horizontal at an angle of approximately 45°.

Each animal was exposed to continuous waves from the transmitter. The average duration of exposure was between two and ten minutes. During exposure, animals were photographed by means of the color television technic of Brown and associates.[12] Ordinary photographs were made as well. Electroencephalograms were recorded before, during, and after exposures. These tracings were made with an 8-channel Grass electroencephalograph connected to 8 electrodes, which were arranged in frontal, temporal, parietal, and occipital positions. The electrodes were made from 20-gauge hypodermic needles. Once modified and connected, the needle was driven in the outer table of the skull. Some records of respiration, blood pressure, pulse rate, and rectal temperature were also made. The animals did not receive any medication before, during, or after exposure. Before exposure, they appeared alert, active, and apparently normal in all respects.

A simple calorimeter system was used to record temperature changes. This calorimeter was a plastic vessel containing water. The total volume of the vessel and contents approximately equaled the average head volume of these monkeys. This was obtained by water displacement. During exposures of ten to thirty minutes at 100 watts, the usual power level used, the temperature changes at the 2 head positions were equal and trivial.

Figure 1 portrays the general assembly as described. In some of the experiments, observations were made with the monkeys in identical cylinders and chairs. Each cylinder was connected to the transmitter through an equivocal loop. Thus, only the person at the transmitter could tell which animal was receiving the radiation during any one exposure. This arrangement served to eliminate some bias in the observers.

OBSERVATIONS

The following protocols are illustrative:

M- (PATRICIA) High head position

Date	*Time*	*Exposure period (minutes)*	*Remarks*
23 Jan.	1245	15	Alternating agitation and drowsiness, plucked at neck, looked up at antenna. Resp. 28/min. Greatly "agitated" at first, more drowsy periods, body tense, with left shoulder and arm forward grasping edge of chair, scratching.
	1315	15	
	1345	15	Body posture the same, drowsy, moves eyes and ears but not head or body on hearing noise. Vocalized at 11 min.
	1415	15	Alternating drowsy and agitated.
	1445	15	Same within 2 min. Recovery in 60 sec. after OFF.
	1515	15	Same, recovery 4 min.
	1545	15	Rigid with frequent limb and head movements.
	1615	15	Drowsy, body in same attitude throughout. 4 min. to recovery after OFF.
	1641	15	Drowsy and still first 7 to 8 min. Began to move about then.

This animal was exposed for a total period of ten hours, seven minutes, thirty seconds in three days. No abnormalities were observed after these exposures.

M-S-216 (TIMOTHY) Low head position

Date	*Time*	*Exposure period (minutes)*	*Remarks*
11 Feb.	1550	10	Lids drooped. Eyes closed, right lid partly. Left internal strabismus. Pupillary size oscillates but right greater than left. Animal is inert, motionless. Flaccid. Lids lift to noise. Pupils react to light. Mouth asymmetric. Does not respond to pressure, pain, or passive movement.
	1645	10	4 min., 20 sec. after ON — left internal strabismus, increase resp., no struggling, ptosis, more marked left lateral nystagmus, slow component to right. Right pupil dilated and then equal, not moving extremities, and tail slightly warm, pupils dilated, not reacting to sound, masticatory movements, eyes fixed and forward. Tail fixed, curved backward. Bilateral ptosis. No response to pinching or deep pain on Achilles tendon. Moved. OFF. Vocalized, nystagmus, ptosis, lids blinked to sound, no response to pinching, hemostat clamped to sole of foot, bilateral, no response. Withdrew when heat (lighted match) held close to each foot.

Four minutes, twenty seconds after the beginning of the exposure, there was a left internal strabismus. The respiratory rate increased, and a bilateral ptosis occurred. There was a lateral nystagmus with a slow component to the right. Next, the right pupil dilated and then contracted, so that the pupils were equal. The animal was motionless. The extremities and tail were warm to the touch. Both pupils dilated, and there was no reaction to sound. Chewing began. The eyes were fixed in forward, conjugate position. The tail was curved and rigid. Bilateral ptosis was noted again. There was no response to pinching or deep pressure on the Achilles tendons. The animal moved spontaneously. The radio frequency was turned off. Nystagmus and ptosis were noted. There was no response when a hemostat was clamped tightly to the skin of the feet. However, the animal withdrew both feet from a lighted match.

In a few minutes after exposure, this animal recovered and responded to stimuli in a usual fashion.

M-R-946 Low head position

Date	*Time*	*Exposure period*	*Remarks*
9 Mar.	1640	2 min., 55 sec.	After 30 seconds both palpebral fissures widened, the animal struggled against the chair and vocalized. At 55 seconds, she began to whimper and there was some increase in salivation. At 1 minute, 55 seconds, both pupils dilated and did not react to light. At 2 minutes, a vertical nystagmus began. At 2 minutes, 30 seconds, the eyes closed tightly, then quickly opened; nystagmus continued. There was some tongue movement. Otherwise there was no movement. The animal did not respond to pain, pressure, or touch. The RF was discontinued at 2 minutes, 55 seconds. The animal's respiration was slow and rectal temperature was 40.2° C. There was no movement. Tone was decreased, and there were no deep or superficial reflex responses. Spontaneous respiration ceased at 1745, 1 hour, 5 minutes after the beginning of an exposure lasting 2 minutes, 55 seconds.

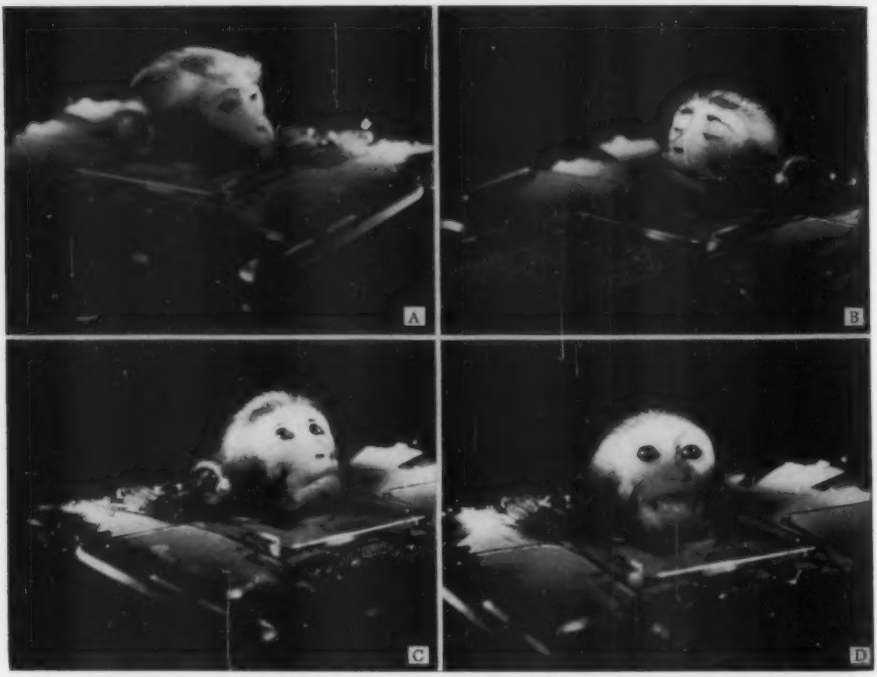

Fig. 2. An animal during stimulation. [A] Immobility and forward gaze. [B] Ptosis and drowsiness. [C] Upward gaze, widening of the palpebral fissures, immobility. [D] Dilation of the pupils, widening of the palpebral fissures, grimace

The clinical signs observed during exposures may be grouped as follows: arousal, drowsiness, akinesia, meiosis, hippus, strabismus, nystagmus, autonomic changes, convulsions, reflex changes, weakness, and hypesthesia. Electroencephalographic changes were also observed.

Arousal, drowsiness, and akinesia. During exposure, all animals became agitated, drowsy, and akinetic. Usually, these changes were observed, in the order named, shortly after the transmitter was switched on. Before exposure, the animal was usually resting quietly in the chair. As exposure began, the animal seemed to stare. His palpebral fissures widened, and his pupils often dilated. He remained still for a few seconds and then moved his head and eyes rapidly from side to side. These side-to-side movements alternated with upward movements. For a time thereafter, the animal became increasingly agitated and struggled against the restraints of the chair. In most cases, this agitation ceased abruptly. The animal became immobile. As movement ceased, the monkey's eyes were open and directed forward or upward (Fig. 2A). The head was either in extension (Fig. 2C) or midway between flexion and extension (Fig. 2B). There was no lateral deviation. The extremities were in flexion and adduction. In this position, all animals seemed less responsive to lights, sounds, pain, touch, or pressure, while some were unresponsive. This akinesia was brief in duration and was ordinarily followed by bilateral ptosis (Fig. 2B) and a drowsy state. In this condition, the animal could be roused promptly by sound or pain, but, after the stimulus ceased, his eyes closed and he

became drowsy again. However, in the ordinary course of the exposure, the animal roused spontaneously. Yet this arousal was usually followed by further periods of drowsing. These, in turn, were interrupted by brisk awakenings. Finally, the periods of drowsing shortened as the periods of arousal lengthened, until the animal seemed awake and even normal. Moreover, if the exposure was discontinued at this point, further changes did not occur. If the animal was then deeply sedated with Nembutal, he could be aroused by further exposure. However, further exposure without sedation was usually followed by staring, akinesia, and bilateral ptosis with drowsiness. Then the pupillary reactions changed, and there were disturbances of eye movements.

Meiosis, hippus, strabismus, and nystagmus. As the exposure continued, the animal usually had bilateral ptosis and seemed drowsy. Suddenly, both eyes opened widely, and the animal stared upward (Fig. 2C). The pupils were equal and small. Then there was rapid blinking. During the last of this, one or the other eye moved inward or outward, as if conjugate control were lost. The palpebral fissures widened abruptly, and, despite the high intensity illumination, the animal's pupils dilated widely. This bilateral dilation was commonly accompanied by a grimace (Fig. 2D). At this time, the animal sometimes made a grunting or gasping sound as respirations accelerated. The pupils then would dilate or constrict in a series of rapid incoordinate changes, after which bilateral dilation occurred. Next, a unilateral strabismus usually appeared. This varied in character but most commonly was internal. Thereafter, nystagmoid jerks and several rapid blinks were noted. The blinking was bilateral and usually coincident with the nystagmoid jerking. These eye movements were either horizontal or vertical and often preceded a repetitive nystagmus. In all cases, the nystagmus usually lasted for several minutes. In 1 instance, vertical nystagmus continued for ten minutes. During nystagmus, the pupils were dilated equally and did not react to light nor was the animal responsive to pain or noise. Sometimes, the nystagmus continued throughout the exposure. In others, the nystagmus ended with a brief period of immobility. In all cases, the eye signs were accompanied and followed by autonomic changes.

Autonomic changes. The nose often became pink before the eye signs began. As the eye movements and pupillary reactions changed, the respiratory rate increased. Occasionally,

M-S-197 (Mimi)

	Date	*Time*	*Head position*	*Frequency*	*Duration*	*Rectal temperature**
1.	25 Feb.	1050	High	387.93	5 min.	38.6° C.
2.	"	?	High	"	10 min.	38.4° C.
3.	"	?	High	"	10 min.	38.0° C.
4.	"	1210	High-Low	"	10 min.	38.0° C.
5.	"	?	High-Low	385.2	10 min.	37.9° C.
6.	"	?	High-Low	"	13 min.	38.0° C.
7.	"	1418	Low	"	10 min.	38.4° C.
8.	"	1455	Low	"	5 min. +	38.3° C.
9.	"	1720	Low	"	10 min., 17 sec.	39.0° C.
10.	"	1750	Low	"	24 min.	39.8° C.
11.	26 Feb.	1756	Low	387.93	10 min.	40.8° C.
12.	"	1852	Low	"	10 min.	40.5° C.
13.	"	1904	Lowest yet	"	5 min., 22 sec.	42.0° C.
14.	"	1936	Low	"	5 min., 30 sec.	41.8° C.

*Immediately after exposure

Fig. 3. Salivation during stimulation

after five minutes' exposure, the rectal temperature rose from an average resting value of 38.5 to 41° C. The temperature response was variable. Sometimes, the hands or feet were moist, and, in 1 animal, the skin of the left arm and right leg seemed relatively warmer. But, in general, the skin of the trunk and extremities was cool to the examining fingers.

Salivation occurred during all exposures. It was noticeable as frothy bubbles during the later developments of the eye signs. When saliva appeared at the lips, the animal usually began to grimace (Fig. 3) and breathing became labored.

Convulsions. After salivation and some respiratory acceleration, the animal occasionally had a generalized seizure. This always began with rapid blinking and bilateral clonic facial movements, accompanied by rapid flexion of the head on the neck and followed by bilateral clonic jerks of the extremities. The average duration of the seizures was two minutes. After the seizure, the animal was flaccid and areflexic. Respiration was usually slowed, while the pupils were equally dilated and without response to light.

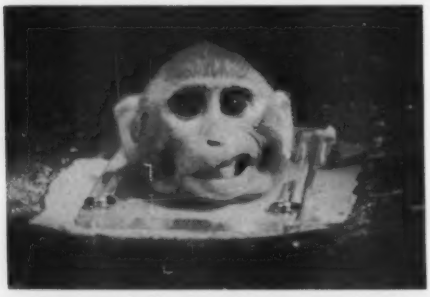

Fig. 4. Right facial paralysis associated with anesthesia to pain in the first and second divisions of the right trigeminal nerve. These signs appeared during stimulation and disappeared forty-eight hours afterward.

Reflex changes. Once the stage of drowsiness appeared, the animal's tendon reflexes were diminished or could not be elicited. In 6 animals, there was a plantar extension on one or the other side. In the postictal state, no reflexes could be elicited.

Motor power. Quadriplegia appeared in 2 animals—1 after two minutes, fifty-five seconds' exposure in the most effective head position. Weakness of the upper extremities was noted in 2 animals after ten minutes' exposure in a similar position. All animals were weak and flaccid in the postictal state; 1 animal had a right facial weakness, central in type, which persisted for forty-eight hours after exposure to 388 mc. in an effective position (Fig. 4).

Sensation. The animals became increasingly less responsive to pinprick during exposure. Usually, the animal did not respond to pain for a short time afterward; 1 animal developed an anesthesia in the distribution of the right fifth nerve. This extended across first and second divisions but did not involve the area along the mandible and was limited by the midline. This animal also had the right facial weakness described above.

Most monkeys reacted to noise throughout the exposure, except during seizures. In fact, a sharp hand clap usually caused the pupils to dilate and was followed by head turning toward the sound. These reactions persisted until the pupils became fixed or a seizure began. Strangely enough, reaction to sound was usually the first sign of recovery after exposure. Yet most animals did not respond to light or movement after the first period of the exposure.

Touch, pressure, and heat evoked responses that varied greatly. No responses to these stimuli were obtained during a seizure or in preterminal states.

Electroencephalographic changes. Scalp electroencephalograms changed during exposure at 388 mc. In most records, changes were evident approximately one hundred forty seconds after exposure began. At that time, a progres-

sive generalized slowing and some increase in amplitude were apparent. There was a predominance of 5-per-second patterns. The record seemed to change quickly from an aroused pattern to one indicative of a drowsy state. These effects were reversible and disappeared within two to three minutes after cessation of exposure (Fig. 5A, B, and C). This sample is typical of the records made. During records, the head was free to move and was not placed in the critical position. No records were made in that placement. The drowsing record was usually coincident with the drowsy appearance of the animal, although some electroencephalographic changes appeared before the relevant clinical signs.

Lethal effects. It was possible to kill monkeys with a few minutes' exposure (two minutes, fifty-five seconds) when the head was fixed with the chin elevated. An exaggerated grimace and forceful closure of the eyes usually indicated that death would occur. Then respiration stopped before heart action ceased.

Postmortem findings and histologic changes. No striking changes were noted in the gross appearance of the brains.

The histologic preparations from 4 brains have been reviewed. In some sections, there are no apparent abnormalities (Fig. 6). In others, there is some fading of the Nissl substance. The section of ventrolateral thalamus illustrates this (Fig. 7). No evidence of thermal effects was found in these sections.

SUMMARY OF OBSERVATIONS

Exposure to a frequency of 388 mc. was followed by neurologic signs. These consisted of agitation, drowsiness, akinesia, and eye signs, as well as autonomic, motor, and sensory abnormalities; 12 convulsions were observed. These began with rapid bilateral blinking and were characterized by bilateral clonic movements.

The clinical signs developed in a sequence. Each phase or stage in the sequence was punctuated by a marked change in awareness and posture. Thus, the sequence usually began with agitation, followed by drowsiness. The drowsiness was suddenly interrupted by a startled expression, which was followed by akinesia. This was followed by a stage characterized by eye signs and autonomic changes.

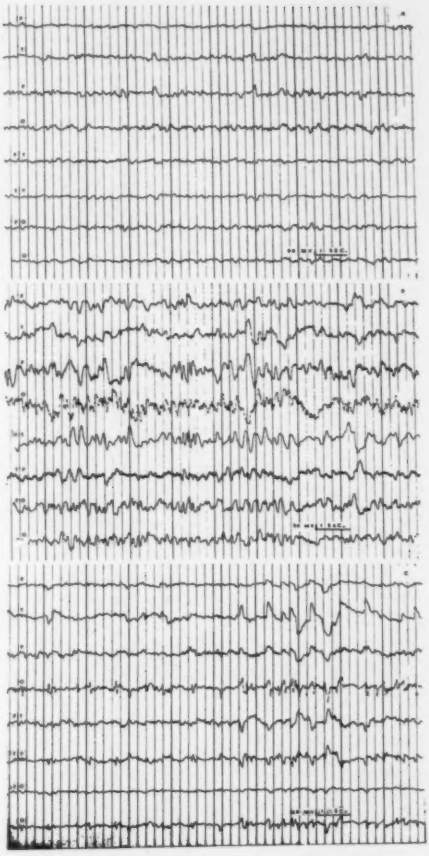

Fig. 5. [A] Normal tracing one hundred forty seconds before stimulation. [B] Tracing four seconds after the beginning of stimulation. Note slow activity. [C] Tracing four seconds after cessation of stimulation

This, in turn, usually ended with either drowsiness or agitation. Thereafter, a seizure might follow. Recovery was invariably preceded by an abrupt heightening of awareness and some agitation. This stage was punctuated by brief periods of drowsiness, which became shorter and less frequent, until the animal appeared normal.

The beginning and end of the clinical sequence were characterized by periodic alterations of awareness.

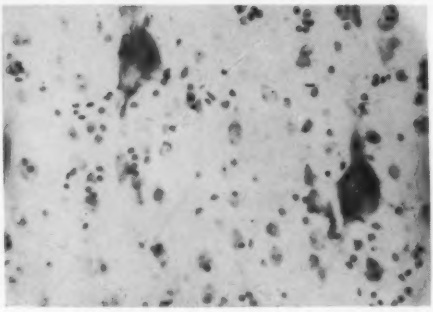

Fig. 6. Motor cortex. Monkey R-946. Total radiation, two minutes, fifty-five seconds. Death occurred at the end of this period. Betz cells well preserved. Small pyramidal neurons showing slight loss of Nissl substance

The majority of the clinical signs disappeared without a trace when exposure was discontinued. Those remaining after exposure usually disappeared in forty-eight hours.

DISCUSSION

Effect of head position. The nature and severity of clinical changes varied with the head position. With elevation of the chin, depression of the occiput, and restriction of lateral movement, the effects were accelerated and exaggerated. However, if the chin was depressed and the occiput elevated while lateral movement was restricted, no changes, except occasional drowsiness, were observed. Nothing more was observed when the animal's head moved freely during exposure. Yet animals with freely moving heads did look up at the antenna more frequently during exposure than at other times. Interestingly enough, Keplinger[13] reported that rats oriented themselves in a wave guide when exposed to 24,500 mc. Likewise, Michaelson[14] said that his dogs turned toward the beam of a 2,800-mc. source.

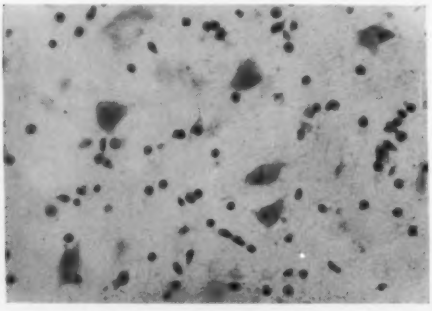

Fig. 7. Monkey S-206. Ventrolateral nucleus of the thalamus. Total radiation, forty-eight minutes. Died during the last part of radiation. Note loss of Nissl substance in the neurons that have been photographed.

Obviously, there is some relationship between head position and the development and extent of the changes observed during radiation. At this stage of investigation, we think that the geometric relationship of the aqueduct of Sylvius to the standing wave pattern in the cavity is critical. In our experience, when the axis of the aqueduct coincides with the axis of the cavity, the clinical signs appear sooner and develop more rapidly. As the long axis of the aqueduct becomes nearly perpendicular to the axis of the resonant chamber, the signs disappear despite long exposures at the effective frequency.

Duration of exposure. The duration of exposure is important or critical in 1 head position. If the chin is up, the occiput down, and lateral movement restricted, duration of exposure is critical. In this position, an exposure of sixty seconds elicits obvious signs, while an exposure of one hundred seventy-five seconds may be fatal. In all other head positions, exposures as long as one hundred seventy-five minutes do not elicit signs, other than drowsiness or some agitation.

Volume of tissue exposed to radiation. When the whole animal, except the head, was exposed for ten minutes at 388 mc., no changes were observed. However, when the head alone is exposed, the changes described above occur.

Nature of effects. During exposure to 388 mc., there were signs of diencephalic and mesencephalic disturbance. The signs occurred individually or in a characteristic sequence. The sequence always began with alternation of arousal and drowsiness. This alternation was related to electroencephalographic signs of sleep and arousal. The initial clinical signs were similar to responses that Magoun[15] has elicited from the rostral reticular system. Indeed, the entire sequence was reminiscent of

responses that Hess[16] evoked during extensive stimulation of diencephalic and mesencephalic mechanisms. Such sequential relationships may indicate some activation of integrated and integrating mechanisms. Also, the rapidity of the sequence may indicate a close functional relationship between the systems influenced by the waves. Perhaps, the radio energy activates mechanisms subserving consciousness, eye movements, tone, posture, and autonomic function?

Finally, there is some histologic evidence of an intraneuronal disturbance. The Nissl substance is washed out in many neurons. Such disturbance may be the result of molecular change subsequent to the electronic activation by a specific frequency (388 mc.).

The authors wish to express their gratitude to Dr. Cosimo Ajmone-Marsan for interpreting the electroencephalograms and to Dr. Igor Klatzo for studying and evaluating the pathologic specimens.

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Intermittent carotid and vertebral-basilar insufficiency associated with polycythemia

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Jack P. Whisnant, M.D.

Since Vaquez[1] and Osler[2] described polycythemia vera, numerous authors[3–9] have documented the fact that neurologic manifestations frequently have a part in the clinical picture of the disease. Thrombosis of a cerebral artery with infarction is the most serious of these and occurred in 10% of 204 patients studied by Lawrence, Berlin, and Huff.[10] However, attention has not been directed to the association of various types of polycythemia and intermittent insufficiency of either the carotid or vertebral-basilar arterial system. Description of this relationship is the primary purpose of this paper. Comments concerning treatment and the pathogenesis of the episodes of insufficiency will be included.

The literature describes many instances of polycythemia vera complicated by cerebral thrombosis. Certain individual case protocols recount recurrent cerebral symptoms probably due to intermittent focal ischemia. Case 61 of Weber[11] had 8 attacks of temporary aphasia during seven weeks prior to hospital admission. Owen[12] wrote of a 64-year-old man who complained of a tingling sensation in the right arm that lasted only five minutes. In a short while, the sensation recurred and spread to involve the right buccal angle. Later the same day, the tingling began again, and, soon, the patient's speech became slurred and inaccurate. All symptoms disappeared in minutes. A diagnosis of polycythemia vera was established. In 1928, Howell[13] described a 29-year-old man who had 6 brief attacks of right hemiparesis the day before permanent right hemiplegia developed. The erythrocyte count was 12,000,000 per cubic millimeter. In a 30-year-old man, Case VII of Oppenheimer,[14] polycythemia vera was said to cause attacks that began with dizziness and blurring of vision and proceeded to convulsion. Noteworthy are 2 cases of polycythemia vera included in a paper by Johnson and Chalgren;[9] 1 patient (Case 3) was a 57-year-old man who had attacks of blindness of sudden onset and short duration in the left eye. In 1 episode, there was paresis of the right side of the body. Later, there was impaired vision in the right eye. Another man (Case 4), 42 years old, had transient attacks of diplopia, then numbness of the left side of the body and poor function of the left hand. Patients reported by Miller,[15] Burris and Arrowsmith,[16] and Nelson and Fazekas[17] also had intermittent attacks of transitory neurologic phenomena. These episodic events were not discussed and were included in the various papers only as portions of case histories. In some instances, the attacks were precursors of cerebral infarction.

At our institution, search for clues to the pathogenesis of intermittent insufficiency of the internal carotid or vertebral-basilar systems has led to more careful hematologic study of patients with these syndromes. At the same time, attention has been directed more closely to neurologic symptoms related by patients with polycythemia vera and other types of polycythemia. Criteria previously described have been used for the diagnosis of intermittent insufficiency in the internal carotid[18] or the vertebral-basilar system.[19] The diagnosis and problem of the polycythemia have been confirmed and reviewed in each instance by one or more members of the Sections of Hematology. All the patients to be described have

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had polycythemia vera, secondary polycythemia, or relative polycythemia.

Polycythemia vera is characterized by elevated whole-blood volume, increased production of erythrocytes, and elevated erythrocyte volume without apparent cause. The same phenomena are observed in secondary polycythemia, but a cause—such as arteriovenous fistula, pulmonary fibrosis, or certain cardiac lesions—can be detected and in some instances corrected. In relative polycythemia, the whole-blood volume is normal but plasma volume is decreased, with relative increase in erythrocyte volume. The range of normal values in Mayo Clinic laboratories is whole-blood volume, 80 to 100 cc. per kilogram of body weight; plasma volume, 40 to 50 cc. per kilogram of body weight; and erythrocyte volume, 36 to 50 cc. per kilogram of body weight. These standards are not absolute, and the results obtained in individual cases must be considered in association with clinical observations, as well as with other laboratory and roentgenologic evidence.

REPORT OF CASES

A total of 22 patients with intermittent cerebral vascular insufficiency associated with the above-described types of polycythemia were observed at the Mayo Clinic during the three years 1954 through 1957. Summaries of 10 of the cases are presented to illustrate the relationship between the 2 disorders. Details of clinical and laboratory investigation not essential to this study have been omitted.

Case 1. A 58-year-old man registered at the clinic February 4, 1955, because of episodes of staggering to the right and double vision. He had been well until the summer of 1954, when several episodes of staggering to the right had occurred. These had begun while he was exerting himself and had lasted only four or five minutes. During December, he had had a number of ten- or fifteen-minute attacks of blurred vision. January 3, 1955, while duck hunting, the patient had complained of several episodes of double vision. Three days later, diplopia had occurred again and persisted. Late in that month, he had had an attack of severe vertigo, nausea, vomiting, and circumoral numbness. On February 6, numbness and impairment of function had affected his right hand for several minutes.

Physical examination revealed left internuclear ophthalmoplegia and veering to the right when he walked in tandem fashion. The blood pressure was 140/90 mm. Hg.

Laboratory findings were hemoglobin 17.1 gm. per 100 cc. of blood; erythrocytes, 5,190,000, leukocytes, 6,000, and platelets, 219,000 per cubic millimeter of blood; hematocrit, 60%; whole-blood volume, 69; and plasma volume, 28 cc. per kilogram of body weight.

A clinical diagnosis of intermittent insufficiency of the vertebral-basilar system with a small intrapontine infarct and polycythemia was made. The hematologist believed this was early polycythemia vera.

In 3 phlebotomies, a total of 1,500 cc. of blood was withdrawn. After that the hematocrit was 45%. No further attacks of vertebral-basilar insufficiency occurred after the second phlebotomy.

Correspondence with the patient's physician during January 1958 indicated that the polycythemia had been controlled with further phlebotomies and administration of radioactive phosphorus and that no further attacks of insufficiency had occurred. The internuclear ophthalmoplegia had persisted.

Case 2. A 65-year-old woman registered at the clinic on January 30, 1957, and immediately was admitted to the hospital. She had been well until 9:30 a.m. on January 25 when, while sitting, she suddenly had stopped talking because she could not think of the correct word. This disability had lasted a minute or two. A few minutes later, standing in the kitchen, she suddenly had lost all ability to move the right hand. The episode had been observed by a relative who had moved the extremity for the patient and described the part as "limp." In three or four minutes, the patient had been normal. At 12:30 p.m. the same day, when sitting at the table eating, the patient had become unable to talk. She had garbled or mispronounced words and had been unable to get the correct one. Minor dysfunction had affected the right hand. She had been put to bed and in half an hour had been talking fairly well. By evening, her condition had returned to normal.

On February 6 and 7, while she was in the hospital, similar episodes occurred.

At admission, physical examination revealed 2 positive signs: dusky appearance of the face and blood pressure of 200/100.

The initial diagnosis was intermittent insufficiency, probably in the left internal carotid system.

Laboratory findings were urinalysis, normal; hemoglobin, 23.5 gm.; erythrocytes, 7,500,000; leukocytes, 11,000; hematocrit, 84%; whole-blood volume, 163 cc. per kilogram; plasma volume, 20 cc. per kilogram; and thoracic roentgenograms, normal.

The hematologist made a diagnosis of polycythemia vera.

Treatment consisted of 3 phlebotomies, 500 cc. of blood being withdrawn at each, and radioactive phosphorus was administered.

The patient has returned to the clinic on several

occasions. The findings from laboratory examination of the blood were normal on March 21, 1957, and have continued so thereafter.

No further attacks of intermittent carotid insufficiency have occurred.

Case 3. A man 43 years old first registered at the clinic January 30, 1950, with the complaint of attacks of numbness and clumsiness of the left hand. During February 1949, his *right* hand had been affected by prickling sensation and dysfunction in several short episodes. After that, he had been well until the summer of 1949, when he had experienced episodes of clumsiness of the *right* hand. In December had occurred the first episodes of numbness and weakness of the left hand. Each had lasted twenty to thirty minutes. On 2 occasions in the next month, the left side of the mouth had sagged and the speech had been slurred. There had been 1 very brief attack of weakness of both legs.

Findings at examination were slight weakness at the left buccal angle, grips normal to —1 (on a basis of —1 to —4, the latter signifying complete paralysis), and alternate motion rate of the hands normal to —1. The blood pressure was 124/84.

Laboratory findings were urinalysis, normal; hemoglobin, 15 gm.; erythrocytes, 4,480,000; leukocytes, 5,900; sedimentation rate, 2 mm. in one hour (Westergren method); and Kolmer test of blood, nonreactive. The cerebrospinal fluid was under normal pressure and contained 2 lymphocytes per cubic millimeter and 25 mg. of protein per 100 cc. The Kolmer test of cerebrospinal fluid was nonreactive. Roentgenograms of the head and chest indicated normalcy. The electroencephalogram showed a symmetrically distributed dysrhythmia, grade 1 (on a basis of 1 to 4, the latter being most severe). A pneumoencephalogram was interpreted as revealing no significant abnormality.

The diagnosis at the time of dismissal was indeterminate.

The patient returned to the clinic during December 1950 and June 1951. He had had a few mild attacks of weakness of the left upper extremity. Examination showed no evidence of progression.

On January 15, 1952, the patient again registered at the clinic. He related that on August 23, 1951, while standing talking, he suddenly had become unable to get the correct word. The right side of the body had seemed weak. He had started walking, but, after a few steps, the right lower extremity had given way and he had fallen to the floor. Five minutes later, he had been normal. In December 1951, a similar attack occurred but recovery required forty-eight hours.

The findings at physical examination were essentially the same as those obtained on previous visits to the clinic.

The blood hemoglobin was 15.4 gm. and the erythrocyte count, 5,060,000. There was no change in the electroencephalogram.

The interpretation of bilateral carotid angiograms was normal. A ventriculogram was interpreted as revealing minimal evidence of an expanding lesion in the left parietal parasagittal area, but, at craniotomy, a tumor was not found.

The patient returned to the clinic in July 1955. During the interval, he had been examined in 2 other hospitals but no diagnosis had been established. Sporadic attacks of severe generalized weakness without change in consciousness had occurred. Each of these lasted a few minutes. A few episodes had been characterized by clumsiness and weakness of the right hand.

Physical examination showed the phenomena on the left side of the body unchanged. The muscle stretch reflexes on the right were graded 3+ (on a basis of —4, which is weakest, to +4, which is strongest), and a Babinski sign was elicited on the right.

A clinical diagnosis of intermittent insufficiency in the vertebral-basilar system with residual damage in the brain stem was made.

Laboratory findings were hemoglobin, 19.4 gm.; erythrocytes, 7,060,000; leukocytes, 11,400; platelets, 866,000; hematocrit, 68%; whole-blood volume, 102 cc. per kilogram; and plasma volume, 29 cc. per kilogram. The electroencephalogram showed a dysrhythmia, grade 2, focal left sylvian.

A diagnosis of polycythemia vera was made by the hematologist. The patient was treated with radioactive phosphorus and phlebotomies (2,000 cc. of blood withdrawn).

In October 1955, the patient returned to the clinic. He had been doing hard physical work and had had no further attacks. There was no longer a Babinski sign on the right. Other findings at physical examination were unchanged. The hemoglobin was 16.4 gm., erythrocyte count, 6,180,000, and hematocrit, 58%. Additional withdrawal of blood was advised, and the referring physician performed it.

The latest examination was made in March 1956. The patient's mood was mildly depressed, but he had had no more attacks of neurologic dysfunction. The polycythemia was controlled. The electroencephalogram showed a dysrhythmia, grade 1, focal left sylvian. Continuation of measures for control of the polycythemia vera was recommended.

Case 4. A man then 73 years old had first registered at the clinic in November 1949. A diagnosis of chronic prostatic hypertrophy, acute thrombophlebitis in the left lower extremity, and polycythemia vera was made at that time. The laboratory investigation of the blood showed hemoglobin, 18.4 gm.; erythrocytes, 6,140,000; leukocytes, 11,000; hematocrit, 69%; whole-blood volume, 124 cc. per kilogram; and plasma volume, 40 cc. per kilogram.

Multiple phlebotomies removed a total of 2,000 cc. of blood, and radioactive phosphorus was administered.

On February 11, 1957, when 81 years old, the patient returned to the clinic and was admitted to the hospital. During the intervening years, the

polycythemia had been controlled by multiple phlebotomies and radioactive phosphorus therapy. On December 21, 1956, he had experienced left hemiplegia that had lasted fifteen minutes. Four days later, he had had another attack of the same type, lasting fifteen to twenty minutes. A third attack had occurred on December 30 and had not remitted.

Physical examination revealed left hemiplegia and left homonymous hemianopsia.

A diagnosis of 2 attacks of intermittent insufficiency in the right internal carotid system followed by cerebral infarction in the right hemisphere was made.

A note from the referring physician stated that the hematocrit was 60% on the day the cerebral infarction occurred.

The polycythemia was controlled by multiple phlebotomies. There was mild improvement in the left hemiplegia with physiotherapy, but the left homonymous hemianopsia persisted.

Case 5. A 73-year-old man registered at the clinic on June 19, 1956, and immediately was admitted to the hospital. He complained of recurrent numbness of the right side of the body. One afternoon early in June, while working on a cultivator, the patient had noticed a sudden onset of numbness in the entire right side of the body and difficulty in moving the right arm and leg. Simultaneously, vision to the right had been impaired. He had been able to drive his car home, and, in an hour, his condition had returned to normal. During the next six days, 5 or 6 similar episodes had occurred. Each attack had lasted fifteen to fifty minutes, and each recovery had been complete.

Findings at physical examination were normal except that the right biceps and knee jerks were slightly stronger than those on the left.

Findings from laboratory examination were hemoglobin, 18.2 gm.; erythrocytes, 7,630,000; leukocytes, 18,000; platelets, 276,000; and hematocrit, 70%.

The diagnosis was intermittent insufficiency of the left internal carotid system and polycythemia vera.

On June 21, 1956, 500 cc. of blood was removed by phlebotomy. Radioactive phosphorus, 4.8 mc., was administered. On July 6, 500 cc. of blood was removed, and the next day the hematocrit was 59%. In the period since admission, the attacks of numbness and weakness of the right side of the body had become increasingly severe, with difficulty in speaking and impairment of vision to the right. More definite hyperreflexia and a Babinski sign on the right began to persist between attacks. Anticoagulant therapy with ethyl biscoumacetate (Tromexan) and bishydroxycoumarin (Dicumarol) was started on July 9. There was 1 attack the next day. On July 11, the prothrombin time was in the therapeutic range. No further episodes occurred. Control of the polycythemia was accomplished gradually, and anticoagulant therapy was discontinued December 10, 1956.

The patient returned in February, April, July, October, and December of 1957. The polycythemia was under satisfactory control, and there had been no further episodes of carotid insufficiency.

Case 6. A 54-year-old man registered at the clinic on July 22, 1955. He complained of having had "dizzy spells" in the preceding year and a half. He had been well until early 1954 when, sitting in a construction office and smoking a cigar, he suddenly had become faint. The cigar had dropped from his mouth, vision had become dim, and nausea as well as generalized weakness had developed. Consciousness had not been impaired. An hour later the patient had been normal. During the year after this, he had had 10 more attacks. Each had been characterized by the sudden onset of a feeling of weakness all over, a whirling sensation, nausea, vomiting, diplopia, dimness of vision, and, on a few occasions, slurring of speech. The total duration of each had been ten to thirty minutes.

In March 1955, the patient's home physician had made a diagnosis of polycythemia vera and, over a five-week period, had performed 3 phlebotomies, removing 500 cc. of blood at each. No more attacks had followed the phlebotomies. Radioactive phosphorus had been administered on June 9, 1955.

At the clinic, physical examination revealed no unusual signs.

Laboratory findings were hemoglobin, 14.5 gm.; erythrocytes, 5,920,000; leukocytes, 5,800; platelets, 107,000; hematocrit, 52%; whole-blood volume, 88 cc. per kilogram; and plasma volume, 42 cc. per kilogram.

A diagnosis of intermittent vertebral-basilar insufficiency and polycythemia vera in control was made. No further episodes of insufficiency occurred.

Case 7. A woman then 43 years old first registered at the clinic during the summer of 1941. During March of that year, she had suffered several episodes of numbness and poor use of the left hand. In one of these, there had been weakness of the left side of the face that lasted an hour. One morning in April, on awakening, she had noted blindness of the right eye. Later that morning she had complained of slight weakness of the left lower extremity and severe weakness and clumsiness of the left hand. By evening, the left side of the body had become normal, but blindness had persisted. A pneumoencephalogram made elsewhere had been interpreted as normal. In May had come another attack of left hemiparesis with recovery, and, later that month, an attack occurred from which she did not recover.

Findings at physical examination were blindness of the right eye (occlusion of the central retinal artery); left hemiparesis, grade 3 in the upper extremity and grade 1 in the lower extremity; and

hyperactive muscle stretch reflexes on the left, with a Babinski sign and diminished response to pin, thermal, and light touch stimuli in the left upper extremity.

Laboratory findings were hemoglobin, 17.5 gm.; erythrocytes, 5,370,000; leukocytes, 11,200; hematocrit, 57%; whole-blood volume, 114 cc. per kilogram; and plasma volume, 48 cc. per kilogram.

A diagnosis of polycythemia vera with a cerebral infarct and thrombosis of the central retinal artery was made.

The polycythemia vera was controlled with multiple phlebotomies and radioactive phosphorus therapy. The patient was last seen at the clinic in July 1957. She had had no further intracranial trouble.

Case 8. A man then 55 years old had first registered at the clinic in 1939 with the complaints of headache and easy tiring. A diagnosis of polycythemia vera was made. Treatment through the years consisted of phlebotomies and administration of radioactive phosphorus. In 1951, the polycythemia vera was found to be well controlled.

The patient entered the clinic again in August 1955, when 72 years of age. Early that year, he had suffered a number of attacks of "lightheadedness" that consisted of a whirling sensation and lasted five to ten minutes. These had come on whether he was standing, sitting, or lying down. In July, while he had been sitting, his head suddenly had dropped forward, the right arm and hand had become useless, and he had been confused and his speech garbled. In thirty minutes, the arm and hand had been almost normal but the speech defect had persisted.

Examination revealed partial afferent aphasia.

The hemoglobin was 16.6 gm., erythrocyte count, 7,330,000, and hematocrit, 58%.

A diagnosis of possible intermittent insufficiency of the vertebral-basilar system and a small cerebral infarct in the field of the left middle cerebral artery was made.

The hematologist commented that the polycythemia vera was out of control. Phlebotomies removed a total of 750 cc. of blood.

The patient returned during April 1956, at which time the polycythemia vera was controlled. He had had no more attacks. There was a residual mild afferent aphasia.

Case 9. A 51-year-old woman registered at the clinic December 4, 1954, with a complaint of attacks of dizziness and impairment of vision. During the year preceding registration, the patient had noted easy fatigability. In November, the first attack had occurred. One afternoon, she had been sitting reading when suddenly she had become aware of a "strange sensation" in the back of her head. She had leaned forward and blacked out. At the return of consciousness, she had been on the floor, blind. She had crawled about the room, finally located the telephone, and called a friend. When the patient had begun to talk, her speech was severely slurred. In an estimated ten minutes, she had begun to vomit and had continued for about ten minutes. Then vision had begun to return, and, in an hour, the patient had been normal. She had not experienced headache or stiffness of the neck. Between the time of the first episode and registration at the clinic, she had had 6 less severe attacks. Each of these had included vertigo, nausea, vomiting, and impairment of vision but not blindness. Each had been sudden in onset and had ended in thirty minutes.

On physical examination, the lips, tongue, cheeks, fingers, and toes had a cyanotic hue.

Laboratory findings were hemoglobin, 17.1 gm.; erythrocytes, 4,880,000; leukocytes, 6,500; hematocrit, 62%; and Kline flocculation test, nonreactive. Thoracic roentgenograms showed in the right upper lobe an oval shadow 4 by 6 cm. and, leading into it from the hilus, 2 shadows 1 cm. wide that had the appearance of vessels. These features were interpreted as signifying a pulmonary arteriovenous fistula. Pulmonary and cardiovascular studies were consistent with this roentgenographic diagnosis.

The clinical diagnosis was intermittent insufficiency of the vertebral-basilar system, pulmonary arteriovenous fistula in the right upper lobe, and secondary polycythemia.

On December 13, 1954, the right upper lobe containing the pulmonary arteriovenous fistula was resected. Recovery was uneventful, and the polycythemia disappeared. Follow-up two years later revealed that there had been no further attacks of vertebral-basilar insufficiency.

Case 10. A 57-year-old man, who had been seen at the clinic during preceding years for a variety of minor complaints, again registered on September 27, 1954, and immediately was admitted to the hospital. He complained that, during the preceding ten days, he had suffered approximately 8 strange attacks that had come on regardless of his position. The episodes had been characterized by burning around the eyes, dysarthria, dysphagia, and tetraparesis to tetraplegia. The onset had taken only thirty seconds, and the duration had been five to ten minutes or forty to sixty minutes. The weakness had been more severe on the right than on the left.

Findings at examination were very slight hyperactivity of the stretch reflexes on the right, a doubtful sign of Babinski, and blood pressure of 140/80.

Laboratory findings were hemoglobin, 18 gm.; erythrocytes, 5,180,000; leukocytes, 6,800; hematocrit, 58%; whole-blood volume, 67 cc. per kilogram; and plasma volume, 28 cc. per kilogram.

A diagnosis of intermittent vertebral-basilar insufficiency and relative polycythemia was made.

During two days of hospital observation, the patient had 3 attacks each day. Several of the attacks were observed to be as the patient had described them. Neurologic examination during an episode gave appropriate findings. In 1 attack, both internal rectus muscles were paralyzed. On

2 occasions, the blood pressure was taken just before and during the onset of attacks. No change occurred in the pressure or in the pulse rate or rhythm.

Because of the increasing severity and frequency of the episodes, anticoagulant therapy with heparin, Tromexan, and Dicumarol was started. The heparin therapy was discontinued after thirty-six hours, and Dicumarol was used for long-term treatment. After 2 phlebotomies removed a total of 1,300 cc. of blood, the hematocrit was 48%. No attacks occurred after anticoagulant treatment was begun.

The patient returned to the clinic in May 1955 and March and September 1956. At the reexaminations, the hematocrit values were 54, 54, and 53%, respectively. Discontinuation of anticoagulant therapy and phlebotomy were suggested, but the patient and referring physician wished to continue treatment with Dicumarol. There had been no further attacks of vertebral-basilar insufficiency.

DISCUSSION

The clinical phenomena observed in the cases described were essentially the same as those seen when polycythemia or focal cerebrovascular insufficiency occurs singly.

The diagnosis of polycythemia must be based on investigation of the blood. Certain symptoms observed in polycythemia vera, such as dizziness and headache, may be part of the pattern of the insufficiency syndromes, particularly those of vertebral-basilar type. The complaint of "dizziness" usually becomes "lightheadedness" in cases of polycythemia or is given some other nondescript designation on careful questioning. This symptom and the vertigo that is so common in vertebral-basilar insufficiency are phenomena of different types. Headache is of little aid in arriving at a diagnosis and must be assessed in relationship to other facets of the individual case. The clinician must rely on a pattern of clinical phenomena in diagnosing the syndromes of intermittent vascular insufficiency and on laboratory data for precise information about the polycythemia.

It is particularly important to note that often the presenting complaints of these patients are the episodic symptoms characteristic of attacks of cerebrovascular insufficiency. This was true in 8 of the 10 cases reported above. Such phenomena as plethora of the lips, cheeks, fingers, and toes, engorgement of the retinal veins, and splenomegaly may lead the clinician to suspect the presence of polycythemia. However, these signs can be minimal or absent. In practically every instance of cerebrovascular insufficiency, a hematocrit value should be obtained to screen for polycythemia. Unusually high values indicate need for further investigation of the hematologic problem. If polycythemia is present, an attempt should be made to define its nature and cause. In Case 9, surgical removal of a pulmonary arteriovenous fistula corrected secondary polycythemia and the patient had no further attacks of vertebral-basilar insufficiency.

Case 3 is of particular interest. The patient was seen at the clinic on several occasions before the syndrome of vertebral-basilar insufficiency was delineated. Many tests were performed in a futile search for an intracranial tumor or aneurysm. On early visits, the hematocrit value was not determined. How long the polycythemia had been present and whether more complete laboratory study would have permitted earlier diagnosis and treatment cannot be stated.

Hemangioblastoma of the cerebellum has been associated with polycythemia. It is rare that such neoplasms are present simultaneously with the characteristic attacks of intermittent vertebral-basilar insufficiency. When symptoms and signs indicative of a gradually progressive, probably expanding lesion in the posterior fossa are present, diagnostic ventriculography must be considered.

This study does not present long-term observations from a series of cases of untreated polycythemia vera for contrast with similar observations of the treated patients. Lawrence, Berlin, and Huff[10] observed a lower incidence of complications among patients whose polycythemia vera was controlled than among those in whom it was uncontrolled. The experience in the 10 cases reported above, and in the remaining 12 cases of this study as well, seems to indicate the importance of quickly controlling the polycythemia and maintaining effective control. In Case 4, control was established and for seven years the patient was well. Then came 2 warning attacks of carotid insufficiency, followed four days later by permanent hemiplegia that began when the hematocrit value was high. Case 8 is similar. Polycythemia vera was controlled, and the patient was well for fifteen years. Then came warning episodes,

and, before the polycythemia vera was controlled again, cerebral thrombosis caused permanent damage to the brain.

When intermittent carotid or vertebral-basilar insufficiency develops in patients with known polycythemia vera, the status of the blood should be checked immediately. If the polycythemia is out of control, it should be treated at once. Administration of anticoagulants for a time may be wise if control of the polycythemia is delayed or difficult. Cases 5 and 10 were instances in which the attacks were so frequent and so severe that it was deemed prudent to administer anticoagulants until the blood findings were normal. Anticoagulant treatment is recommended when attacks of intermittent insufficiency are not relieved by prompt control of the polycythemia or when these cerebral symptoms persist after control of the polycythemia.

The above report of 10 cases documents the association of attacks of intermittent carotid or vertebral-basilar insufficiency with polycythemia. One can only speculate concerning the pathogenesis of such episodes as well as of those seen in patients who do not have polycythemia. Transitory constriction of cerebral blood vessels (vasospasm) was the popular explanation for the condition for many years. Severe atherosclerosis of the vessels observed at necropsy after a course of such events, with the concomitant theoretic decrease in vascular elasticity, absence of any significant correlation of the attacks with stress, and failure of various types of vasodilator therapy to eliminate the episodes have all contributed to the decreasing popularity of the "vasospasm" theory.

Another explanation is transient systemic hypotension with relatively more severe ischemia of brain distal to a permanently narrowed segment of vessel. Corday, Rothenberg, and Putnam[20] recorded their experience in producing an animal preparation of this kind and showed that the theory is possible experimentally. Recently, Meyer[21] reported that reduction of blood pressure in the monkey after partial occlusion of the middle cerebral artery regularly produces infarction in the tissues that vessel should supply. The clinical association of hypotension with signs of focal brain dysfunction has been noted in the literature for decades.

Whether the occurrence of transient hypotension produces transient ischemic attacks in very many instances or whether it has any statistical importance in the over-all problem of stroke is a question yet unanswered. Seldom is the blood pressure actually recorded just preceding or at the onset of either intermittent insufficiency or permanent damage to the brain. Meyer and associates[22] observed focal changes in the electroencephalograms of human beings while compressing the ipsilateral carotid artery and tilting the patient up. The tilting was accompanied by a significant drop in the blood pressure. In a different kind of clinical study, Adams and Vander Eecken[23] were unable to reproduce attacks of insufficiency by putting the patient on a tilt table. Weiss and Froelich[24] were unable to produce electroencephalographic changes in subjects with carotid or basilar insufficiency by rapid tilting alone. With tilting plus unilateral carotid compression, they produced electroencephalographic changes in patients with syndromes of cerebrovascular insufficiency in the same proportion as in patients of a control group matched in age and sex.

Eastcott, Pickering, and Rob[25] reported that lowering the blood pressure did not precipitate attacks in a patient who was subsequently proved to have a partial occlusion of an internal carotid artery. In a previously reported[26] and an unreported case, one of us observed the blood pressure just before and during the onset of a typical attack. In neither instance did the blood pressure change from the value consistently obtained in that patient. In Case 10 of this study, the blood pressure taken just before and during the onset of 2 separate attacks did not change nor did the pulse rate or rhythm.

These observations, together with the facts that strokes seldom occur in patients receiving antihypertensive therapy at the clinic and that less than 30% of patients with cerebral infarction have any detectable form of heart disease, make us reluctant to accept the theory that transient episodes of systemic hypotension actually cause intermittent cerebrovascular insufficiency in most instances.

Temporary occlusion of a brain vessel by tiny emboli from a distant source is another possible cause of the attacks. But no evidence

of a cardiac lesion or other site of origin of emboli can be discovered in a majority of the patients, nor is there evidence of embolic phenomena in other parts of the body. Also, while there may be minor changes in the symptomatology of the various attacks suffered by a patient, the pattern of events is remarkably similar through successive attacks in the individual patient. It seems unlikely that emboli from a distant source would so consistently follow the same path in consecutive episodes of insufficiency. These observations tend to eliminate this mechanism as a likely one except in unusual instances.

In the cases reported in this paper, it appears likely that there is at least some partial cause and effect relationship between the polycythemia and intermittent cerebrovascular insufficiency. Brown and Giffin[27] demonstrated that there was increased viscosity of the blood, and Kety[28] showed that there is marked decrease in cerebral blood flow and increased vascular resistance in polycythemia. These factors enhance the tendency toward the formation of thrombus. It appears appropriate to speculate that the increased tendency toward formation of thrombus can play a part in the pathogenesis of individual episodes of cerebrovascular insufficiency. Whether the short attacks terminate because of disintegration of a fragile early thrombosis or because of the rapid opening of effective collateral channels cannot be stated. Observation of many cases, including arteriographic study, indicates that in many instances the main vascular channels open again. In such instances, it is logical to presume that failure of opening of collateral flow cannot constitute the only defect, as the flow through the main vessels would prevent episodes of insufficiency. Therefore, the association of intermittent cerebrovascular insufficiency and polycythemia appears to supply one more bit of evidence implicating some part of the mechanism of thrombosis in the pathogenesis of the episodes of insufficiency.

SUMMARY

Attention is drawn to the association of polycythemia and focal cerebrovascular insufficiency; 22 patients known to have this combination of disorders have been observed at the Mayo Clinic in the years 1954 through 1957, and 10 of the cases are described in sufficient detail to illustrate the variety of problems that occur. It is emphasized that [1] the initial important phenomenon occurring in a patient with polycythemia can be an attack of insufficiency in the carotid or vertebral-basilar system; [2] it is necessary to examine the blood for polycythemia in every patient with focal cerebrovascular insufficiency; [3] the type of polycythemia should be determined, as specific therapy may be indicated (surgery for pulmonary arteriovenous fistula); [4] when focal cerebrovascular insufficiency occurs in patients known to have polycythemia, the polycythemia should be controlled as rapidly as possible; and [5] it may be necessary to administer anticoagulants for a variable period, depending on the frequency and severity of the episodes of focal cerebrovascular insufficiency.

The concepts of the pathogenesis of intermittent insufficiency in the carotid and vertebral-basilar systems are briefly reviewed. The clinical evidence of polycythemia as a factor in pathogenesis is discussed.

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Meningeal tumors with extracranial metastasis

A clinicopathologic report of 2 cases

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NUMEROUS CASES of metastasis of primary intracranial tumors to extracranial sites have been reported, but only a small proportion have been entirely acceptable. In a review of 48 cases cited from the literature up to 1952, Winkelman, Cassel, and Schlesinger[1] concluded that only 9 cases were valid—1 case of malignant hemangioendothelioma[2] and 8 primary meningeal tumors;[3–8] one of the meningeal tumors that they included, however, was most probably a case with direct extracranial extension, rather than metastasis.[8] Since 1952, there have been 12 additional well documented cases of meningeal tumor that metastasized to extracranial sites.[9–19] A further case of meningioma in which metastasis to the liver occurred was reported by Shozowa,[20] but the tumor was not described in detail or illustrated. The salient features of the cases regarded by the author as valid are summarized in the table.

Among 803 cases of meningeal tumor at the Armed Forces Institute of Pathology, there were 2 in which extracranial metastasis occurred. A report of them follows.

CASE REPORTS

Case 1. (AFIP Acc. 584563) The initial symptoms in a white man aged 19 years appeared in December 1942 in the form of a grand mal seizure, which was ushered in by a sensation of light in the left visual field followed by a sensation of dizziness. The seizures continued at approximately six-week intervals and were usually preceded by a sensation of flashing red light with a white center in the left visual field. The patient also complained of occasional occipital headaches and reduction of vision in his left eye.

He entered hospital in April 1944. His mental status was found to be apparently normal. Funduscopic examination disclosed bilateral papilledema of 1 diopter. There was an homonymous left inferior visual field defect. Slight left facial weakness of central origin was noted. Station and gait were normal, and tests of coordination were satisfactorily performed. The deep muscle reflexes were brisk and equal. No pathologic reflexes were elicited. Sensibility was fully preserved. Roentgenograms of the skull revealed thickening of the right occiput, with a radiating "sunburst" effect in the inner and outer tables of the skull, which was regarded as diagnostic of meningioma. A pneumoencephalogram indicated the presence of a right occipitoparietal tumor.

Right parietooccipital craniotomy was performed on May 31, 1944. A tumor was located on the right side of the sagittal sinus, and extending into it from the internal surface of the skull were spicules of bone. Because of excessive loss of blood, the operation was terminated without removal of any of the tumor. Reexploration was done on October 18, 1944. The dura, which was greatly thickened, was incised about 5 cm. to the right of the midline. Firmly attached to the reflected dural flap was a tumor about the size of an orange, which involved the sagittal sinus; for this reason, only a part of it was removed. Convalescence was uneventful, and the patient was discharged from hospital on anticonvulsant medication.

Six months later, he spent a few days in a hospital for control of the seizures, which began in his left fourth and fifth fingers, "marched" in jacksonian fashion, and culminated in a generalized convulsion. In 1947, active pulmonary tuberculosis of the right upper lobe was found and he was again hospitalized. The tuberculosis responded well to therapy, but the seizures became increasingly difficult to control. Defective insight, faulty judgment, ideas of reference, and impairment of memory for past events gradually set in. He was found dead in bed on December 19, 1952, the outcome apparently of a convulsion.

From the Armed Forces Institute of Pathology, Washington, D. C.

Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 18, 1959.

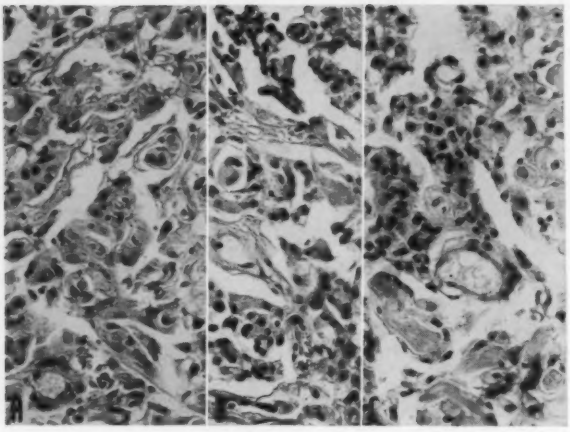

Fig. 1. *(Case 1)* Meningeal [A], pulmonary [B], and mediastinal [C] tumors. Note the striking similarity in cellular constitution and pattern in the primary and secondary tumors. All × 305. Hematoxylin-eosin stain

Postmortem observations. A firm tumor, 7 x 4 x 4 cm., was situated between the occipital lobes and was attached to the dura. The cerebral convolutions immediately adjacent to the mass were atrophic, and the sagittal sinus appeared to be obliterated.

Examination of the lungs revealed 3 nonencapsulated tumors in the anterior part of the left lower lobe. They were immediately subpleural, and their cut surfaces were firm and gray-white; 2 similar tumors were also found in the right lower lobe. An encapsulated tumor, 5 x 4 x 2.5 cm. and of similar appearance, was present in the left posterior mediastinum.

Microscopically, the meningeal tumor was composed of fairly large cells, with many indistinct cytoplasmic borders, arranged in sheets and occasional whorls (Fig. 1A). Smaller cells of similar structure were also found. There were a few concentrically laminated hyaline structures, some of which had a calcified core (psammoma bodies). No mitotic figures were seen. The tumor was rather sparsely vascularized. Sections from the tumors in the lungs and mediastinum (Fig. 1B and C) revealed a highly similar cellular composition and structure. A reticulum stain revealed only sparse reticulum fibrils, primarily in the vicinity of blood vessels. Changes observed in the upper lobe of the right lung were compatible with those of healed tuberculosis.

Case 2. (AFIP Acc. 211158) A white man, aged 55 years, had a chronic illness that brought him to hospital in 1940 complaining of dizziness, diplopia, bilateral frontal headaches, dysphagia, and a sensation of formication in the fingers of the left hand. At that time, he had a moderate arterial hypertension and left hemiparesis. A diagnosis of cerebral thrombosis was made. His condition gradually improved, and, after two months, he was discharged from hospital. Subsequently, he was fairly well except for limitation on activity imposed by the left hemiparesis. His blood pressure remained around 170/100.

He was again admitted to hospital on August 27, 1947, because of sudden loss of consciousness during the preceding evening. He was comatose. His pupils were small, round, regular, and nonresponsive to light. Deep muscle reflexes were equal and slightly hyperactive. There was ankle clonus and a positive Babinski response bilaterally. Death occurred eight hours after admission to hospital.

Postmortem observations. Extensive subarachnoid hemorrhage, presumably due to rupture of a berry aneurysm, was noted. Within the dura just to the left of the midline in the midfrontal region was a firm, gray-white spherical tumor, 2 cm. in diameter. It had indented but not invaded the left cerebral hemisphere. The periphery of the upper lobe of the right lung contained a circumscribed pale gray nodule, 8 mm. in diameter. Its cut surface was firm.

The meningeal tumor was composed chiefly of spindle cells with elongated nuclei, arranged in interlacing bundles and whorls (Fig. 2A and B). Scattered here and there were clusters of meningothelium-like cells and numerous laminated structures (psammoma bodies) showing hyalinization and calcification. Collagen and reticulum fibers were sparse. No mitotic figures were seen. Histologically, the tumor beneath the thickened pleura was identical with that of the meninges (Fig. 2C and D). It was sharply delineated from the surrounding lung parenchyma.

DISCUSSION

In the 2 cases presented, the histologic appearance of the pulmonary and mediastinal tu-

mors was such as to identify them as of intracranial origin. In neither case did the pulmonary tumor resemble, even remotely, primary epithelial bronchogenic tumor, malignant mesenchymoma, or malignant or benign mesothelioma. Malignant mesenchymoma is a complex tumor that has 2 or more structural components of mesenchymal origin. While these tumors contain areas compatible with fibrosarcoma, their histologic appearance is decidedly different from that observed in the meningiomas presented in this report. The mesotheliomas have been the subject of considerable argument, with some authors doubting that they exist.[21] Stout,[22] however, has described both a malignant and a benign form of mesothelioma of the pleura. The malignant mesothelioma was characterized by centrifugal growth over broad areas of pleura, with the formation of tracts and spaces lined by cells resembling the lining of serous membranes when their cells are swollen from irritation. The benign solitary fibrous mesothelioma of the pleura was composed of patternless spindle cells, collagen, and reticulin fibers. "Such disorderliness and lack of organized pattern," Stout remarked, "sets this tumor apart from all other fibrous growths, and makes it relatively easy to recognize." It is obvious that the tumors described in this report are radically different from primary mesenchymal tumors.

Autopsies performed in both the cases presented were sufficiently complete to rule out the possibility of a primary tumor elsewhere than noted. From the standpoint of the clinical history in Case 1, symptoms of a meningeal tumor appeared ten years before death, further establishing the primacy of the intracranial tumor. In Case 2, both the meningeal and pulmonary tumors were apparently asymptomatic and were discovered incidentally at autopsy.

The sites of extracranial metastases from meningeal tumors, as noted in all the cases listed in the table, are indicated in Figure 3. The preponderant sites of metastasis are the lung and pleura. Of the recorded cases, 2 are exceptional in that metastases were found only in the cervical lymph nodes,[11,17] which they had reached by way of regional lymphatics, following direct extension of the tumor through the skull into the subcutaneous tissue.

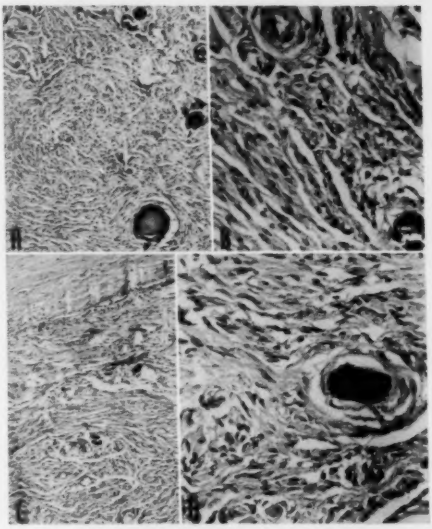

Fig. 2. *(Case 2)* [A and B] Primary meningeal tumor. Note typical meningioma pattern and psammoma bodies. [C and D] From the pulmonary metastatic tumor. Note the attachment of the tumor to the thickened pleura. The appearance of the meningeal and pulmonary tumors is virtually identical. A and C, × 98; B and D, × 305. Hematoxylin-eosin stain

Metastases occurred in the liver and/or kidney in 5 cases. These cases were all described as fibrosarcomas or in other terms denoting some histologic evidence of malignancy. It is believed that the metastases to the liver and kidneys were blood-borne from pulmonary tumors, which were also noted in 2 cases. In the 3 cases in which pulmonary tumors were not noted, it is presumed that pulmonary metastases were overlooked or had possibly undergone regression.

In order that blood-borne metastasis may occur, tumor cells must have access to vascular channels. In explanation of the attainment of such access, we would point out the particular ability of meningiomas to involve contiguous structures by a process of permeation. Such permeation may occur in both directions from the origin of the tumor in the dura, resulting in infiltration of the skull or penetration of the brain along the Virchow-Robin spaces. In-

TABLE

DATA ON 20 METASTATIC MENINGEAL TUMORS

Authors	*Age*	*Sex*	*Duration**	*Location*	*Operations prior to discovery of metastasis*	*Site(s) of metastasis*	*Diagnosis as given by author*
Cushing and Eisenhardt[3]	35	F	5 yr.	Left fronto-temporal	17 operations over 13 years	Lung	Fibrosarcoma
Jurow[6]	72	F	?	Parasagittal, vertex	None	Lung, pleura	Transitional meningioma with psammoma bodies
Hamblet[5]	42	M	2 mo.	Parasagittal	None	Liver	Arachnoidal fibroblasotma
Russell and Sachs[7]							
Case 1	33	F	3½ yr.	Right parieto-occipital, parasagittal	Thrice, with intervals of 1 and 1½ yr.	Lung, pleura, lymph nodes, lumbar vertebra	Malignant arachnoid fibroblastoma
Case 2	38	F	15 yr.	Left temporal lobe	Twice, with an interval of 13 yr.	Liver, lung, mediastinum	Meningioma, then fibrosarcoma
Case 3	12	F	6 yr.	Right occipital, parasagittal	Thrice, with an interval of 2 mo.	Pleura	Poorly differentiated fibrosarcoma
Dublin[4]	83	M	?	Right parieto-occipital, parasagittal	None	Lung, pleura	Fibrosarcoma
Winkelman, Cassel, and Schlesinger[1]	54	M	41 mo.	Parietal, parasagittal	Thrice, with intervals of 3 yr., and 2 mo.	Lungs	Fibrosarcoma
Cross and Cooper[10]	52	M	7 yr.	Left parietal, parasagittal	Thrice, with intervals of 2 yr. and 4 yr.	Lungs	Malignant meningioma
Christensen, Klaer, and Winblad[9]							
Case 1	38	M	24 yr.	Parasagittal	Twice, with an interval of 7 yr.	Liver, kidney	Fibrosarcoma
Case 2	40	M	13 yr.	Parasagittal	Once	Lung	Meningioma
Swingle[15]	39	M	8 mo.	Right parasagittal	Once	Lung	Meningiosarcoma
Zülch, Pompeu, and Pinto[16]	47	M	22 yr.	Right fronto-parietal	Once	Liver, lungs, kidney	Malignant meningioma
Lima[11]	55	M	16 yr.	Parasagittal	Six times	Cervical lymph node	Meningioma
Laymon and Becker[17]	72	M	7 yr.	Right parietal	None	Cervical lymph node	Meningioma
Rosen and Branch[13]	44	M	4 mo.	Right temporal	Once	Liver	Meningeal sarcoma
Simpson[14]	56	F	3 yr.	Left frontal parasagittal	Twice, with an interval of 1 yr.	Lungs	Malignant meningioma
Ringsted[12]	50	M	13 yr.	Parasagittal	Once	Lungs, pleurae	Meningioma
Shtern[18]	39	M	?	Parasagittal	None	Lungs, plura	Meningioma
Gibbs[19]	23	F	3 yr., 8 mo. (to death)	Parasagittal	Once with finding tumor	Lungs	Meningioma
Present cases							
Case 1	21	M	10 yr.	Right occipital, parasagittal	Twice, with interval of 5 mo.	Lungs, posterior mediastinum	Meningioma
Case 2	62	M	?	Left frontal parasagittal	None	Pleura	Meningioma

*Duration of symptoms at time of initial surgery or death

volvement of dural sinuses by meningiomas is common. This was observed, for example, in 14 per cent of the 235 meningiomas studied by Simpson.[14] Actual invasion of a dural sinus, with tumor present within the sinus lumen, has not been observed in any of the recorded cases of metastatic meningioma. The intimate relationship of pacchionian granulations to sinus lumina in normal histology is such, however, as to suggest that ample opportunity exists for actual invasion of the sinus and the subsequent production of tumor emboli.

Introduction of tumor emboli into vascular channels as the result of surgical intervention has been suggested as a mechanism of initiating metastasis. Such a possibility could be ruled out in 5 of the cases listed in the table, as no intracranial exploration was carried out during the patient's lifetime.

SUMMARY

Tumors arising in the meninges and metastasizing to the lungs in 2 patients are reported. In 1 of them, metastasis occurred also in the posterior mediastinum. The primary tumors and metastases in both cases had histologic features characteristic of meningioma of essentially benign nature. These 2 cases bring the total of recorded verified metastatic meningeal tumors to 22.

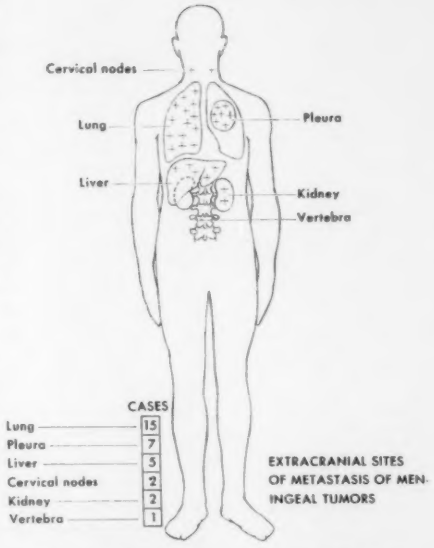

Fig. 3. Extracranial sites of metastasis in 22 cases of meningeal tumor listed in table

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Study of septal stimulation and ablation in the macaque monkey

Charles L. Votaw, M.D., Ph.D.

In recent years, there has been considerable interest in the rhinencephalic and/or limbic structures of the telencephalon because of the possible relationship of these areas to affective behavior. The septal area, an integral part of these systems, lies just anterior to the rostral end of the diencephalon and, by its position, is well located to act as a relay station for both ascending and descending impulses. Research has shown that these septal areas are part of a pathway involved in the relaying of nonspecific sensory information to the rhinencephalon. These areas also receive impulses from the fornix, which has often been considered to be chiefly an efferent hippocampal pathway.

If the septal area is a part of the neural mechanism involved in affective behavior, impulses passing through it may be concerned with movements that accompany such behavior. Therefore, an investigation was planned to ascertain whether any movement would result from electrical stimulation of the septal nuclei. If motor responses should occur on stimulation, the neural pathways mediating these functions should warrant study.

The areas of direct concern in this paper are those of the medial and lateral septal nuclei as described by Lauer[1] in his study of the macaque forebrain. Not considered in this study, but a part of the septal area, are the nucleus of the diagonal band of Broca, the nucleus accumbens, the bed nuclei of the anterior commissure and stria terminalis, and the nucleus septalis triangularis. This septal area is located in the subcallosal region of the medial wall of the hemisphere, posterior to the frontal cortex and superior to the olfactory tubercle. It covers an area anterior and superior to the anterior commissure. The medial and lateral septal nuclei are contained in this area, the lateral occupying the greater portion of the space. The medial, which is considerably smaller than the lateral, lies ventral, caudal, and medial to the lateral septal nucleus.

Materials and Methods

Aseptic surgical procedures were carried out on 5 monkeys (Macaca mulatta). The animals were unselected as to sex and had not been subjected to previous experimentation. Preoperative testing showed these monkeys to be healthy and neurologically asymptomatic. The animals had not received training of any sort before the procedures were carried out. Ether anesthesia was used for all operations.

In monkey No. 1, exposure of the left septal area was accomplished by a frontal craniectomy and removal of a part of the prefrontal cortex just anterior to area 6. In this manner, the lateral ventricle was opened and the septal area was revealed on the medial wall of the ventricle. A unipolar stimulating electrode was then placed directly on the septal area so that the region could be electrically stimulated. For this and all the following procedures, a Grass Co. S4 stimulator was used, with a rectal plug as the indifferent electrode. A frequency of 40 stimulations per second and a pulse duration of one millisecond were used throughout all experiments. The stimulus strength varied from 3 to 10 volts. The animal was closely observed for any movements resulting from the stimulation, and motion pictures were taken. After three weeks, a similar stimulation was attempted on the right side. However, technical difficulties precluded stimulation of the right nuclei in this animal.

The septal regions of monkeys No. 2, 3, and 4 were stimulated with the aid of a No. 4 Lab-

From the Laboratory of Comparative Neurology, Department of Anatomy, University of Michigan, Ann Arbor.

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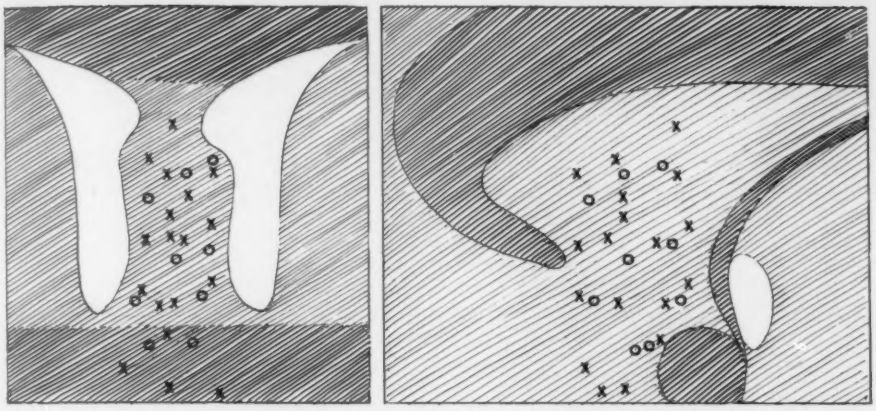

Fig. 1. Frontal view *(left)* and sagittal view *(right)* of the septal area. X's represent the points stimulated which produced movement and O's, the points stimulated after section of the fornix and which then did not produce movement.

Tronics stereotaxic instrument. The coordinates of the electrode were obtained before the procedure by fitting the head of an autopsied animal, with the septal area exposed, into the machine and taking the readings directly. Stimulation and recording of any possible movement were carried out as before. In these cases, both sides were stimulated during the same experiment.

In the remaining animal, monkey No. 5, the fornices were completely severed by means of 2 parietal craniectomies, 1 for each side, performed three weeks apart. A part of the parietal lobe was removed to provide entrance to the lateral ventricle and to reveal the posterior part of the hippocampus and the fornix. Two months after these procedures, the septal area was stimulated bilaterally with an electrode that had been placed with the aid of the stereotaxic apparatus.

After stimulation, lesions were placed in the septal region of all animals as a part of each procedure. The septal area was completely removed from the left side in the case of monkey No. 1. In the remaining animals, electrolytic lesions were made at all points where movement had been obtained.

After completion of the stimulation and ablation parts of each experiment, the operative wound was surgically closed and the animal allowed to recover from the anesthesia before being returned to his cage. Each animal was observed daily to the time of sacrifice for any changes of behavior resulting from the lesions.

Survival times varied from sixteen days to four months. All animals were sacrificed with an overdose of a barbiturate anesthetic (Evipal), and the bodies were immediately perfused intracardially with a solution of 10% neutral formalin. The brains were then removed and fixed in formalin. Microscopic slides of each brain, including the brain stem, were prepared according to the Marchi technic as modified by Swank and Davenport.[2] The microscopic slides defined both the exact electrode position and the location of the degenerated myelin resulting from the lesions.

EXPERIMENTAL OBSERVATIONS

Various points, illustrated in Figure 1, were stimulated during the several operations in the 5 monkeys. The locations of these points were confirmed by a study of the microscopic slides. Adequate stimulation produced a gross type of muscular movement of the face and upper extremities. The movements were bilateral but were much stronger in the face region on the side of the stimulation. They consisted of partial closing of the interpalpebral fissure, flaring of the external nares, retraction of the corners of the mouth, internal rotation and

flexion of the shoulders, flexion of the elbows, and closing of the fists. When the stimulated point was more inferior in the septal region, the movements of the upper extremity tended to be prominent. Other than this, there was no obvious localization pattern.

In monkey No. 5, in which the fornix had been completely severed on both sides, stimulation of the septal area did not result in movement of any kind. Here, and in the previously described cases, however, constant stimulation at the higher strengths of stimulus resulted in a type of arousal of the animal. He appeared as if he were coming out of the anesthesia. When, however, the stimulation ceased, he returned to the previous anesthetic level without additional anesthesia.

When electrodes were oriented in the monkey brains by stereotaxic equipment, lesions were placed at those points at which stimulation caused movements. These lesions were small and were made in each septal area but in no case were they bilaterally symmetric. In this group of animals, no differences were noted between the preoperative and the postoperative behavior pattern. The monkeys reacted in their home cages like normal monkeys who had not undergone any surgery. They had no observable motor defects, moved and climbed about well, and presented no problem in feeding or postoperative care.

The entire left septal area and the anterior third of the right septal area were removed from monkey No. 1, in which the septal areas had been exposed directly. In this animal, the middle and posterior thirds of the right septal area were not damaged but there was a large lesion in the head of the left caudate nucleus and in a portion of the prefrontal cortex on both sides. This animal, when observed postoperatively, moved incessantly, stopping only an instant to make a quick observation. No other abnormality of behavior was noted. His reaction to being captured was that of a normal monkey.

In addition to providing the locations of points of stimulation, the Marchi material showed the position of the degenerated tracts resulting from the lesions that were placed during the operative procedures. Such degeneration was found in 3 of the 5 animals; in monkeys No. 2 and 4, it resulted from stereotaxically placed lesions and, in the third animal (monkey No. 1), was related to the direct removal of the left area.

It may be surmised that any lesion of the septal area will destroy a large proportion of the precommissural fibers of the fornix. If the lesion extends to the posterior regions of the septal area, the postcommissural fornix fibers also become involved. In the experimental material, degeneration granules were followed from the area of the lesion, over the anterior commissure, downward along the postcommissural fornix, and into the hypothalamic nuclei to end mostly in the mamillary nuclei. In one case, degeneration was also found in the medial forebrain bundles, but this was due to direct involvement of the tract in the lesions. Though such degeneration was present, it could not be determined with certainty whether it was due to destruction of the cells of the septal area or of the fibers passing through this area.

Of more direct significance is the observation that lesions of the septal area and/or fornix fibers cause a degeneration in a posterior direction along the body of the fornix. These granules were followed into the fimbria along the entire length of the hippocampus. Estimation of the total amount of degeneration present indicated that the septal area discharges uniformly to all parts of the hippocampus. The fibers enter the alveus from the fimbria (Fig. 2C) and then turn off to end in all zones of the stratum lucidum and polymorphic cell layer of Ammon's horn and among the polymorphic cells of the dentate gyrus. They tend to be more concentrated in zones CA_3 and CA_4 of Lorente de No.[3]

A more detailed description of the degeneration is warranted for monkey No. 1, from which the left septal area was removed completely. The location of the degenerated regions is illustrated in Figure 2. It should be remembered that, in this monkey, there were also lesions of the left caudate nucleus and the prefrontal cortex of both sides. However, a rather large amount of degeneration can be followed from the area of the septal lesion (Fig. 2A) into the body of the left fornix. Approximately 30 to 40% of the total number of fibers in the body of the fornix were degenerated. At this point, a very small number

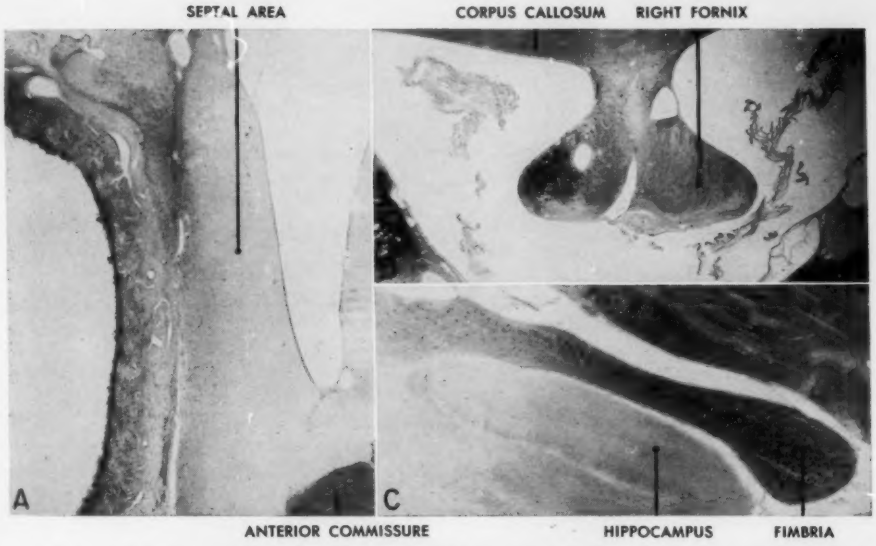

Fig. 2. Photomicrographs of the Marchi material from monkey No. 1, in which the complete left septal area was removed. [A] Lesion in the left septal area (× 13). [B] Major degeneration (black granules) in the body of the left fornix just posterior to the septal area (× 13). [C] Degeneration granules in the left fimbria, turning out to the alveus (× 40)

of degenerated fibers were present in the body of the right fornix (Fig. 2B). As this degeneration was followed posteriorly, a few fibers crossed beneath the corpus callosum. However, a large majority of the fibers remained ipsilateral to the side of the lesion. There was uniform distribution of the fibers to the hippocampal formation of each side.

In résumé: stimulation of the septal area produces facial and upper extremity movements; section of the fornix eliminates the movements obtained from septal stimulation; lesions that include a large portion of the septal area but also the frontal cortex adjoining this area may cause a hyperkinetic state in the animal; and, following lesions in the septal area, there is a prominent degenerated path that is evidently afferent with respect to the ipsilateral hippocampus.

DISCUSSION

Stimulation of the septal area of experimental animals has produced many types of responses. Thus Kabat, Magoun, and Ranson,[4–7] Hodes and Magoun,[8] and Gloor[9] have reported changes in blood pressure and respiratory rate and depth, contraction of the bladder with micturition, piloerection, and changes in size of the pupils secondary to septal stimulation in a cat. Andersson[10] obtained cold defense reactions from such stimulation in the goat. Olds and Milner[11] concluded from self-stimulation experiments in the rat that there is a pleasure-reinforcing center located in the septal area, and Trembly[12] noted enhancement of pleasure reactions resulting from electrical and chemical stimulation of the septal area in the cat. In addition to the autonomic responses obtained in cats, Hodes, Peacock, and Heath[13–16] found that stimulation of the septal area produces facilitation and/or inhibition of both reflexly and cortically induced motor movements.

Since stimulation of the septal area appears to affect somatic and visceral components of the efferent nervous system, as well as to cause certain affective responses in the animal, it is not surprising that stimulation of the same area causes contraction of voluntary muscles. Trembly[12] noted that stimulation caused a

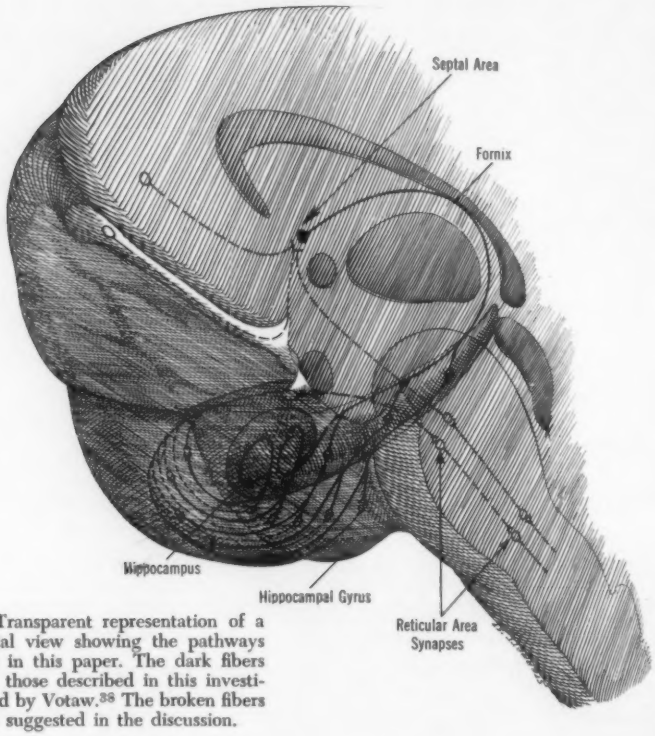

Fig. 3. Transparent representation of a left medial view showing the pathways discussed in this paper. The dark fibers represent those described in this investigation and by Votaw.[38] The broken fibers are those suggested in the discussion.

turning of the head in conscious cats. The movements obtained in the present group of experiments were of a generalized nature, there being only slight suggestion of a localization pattern. This type of motion can logically be assumed to be the type that would accompany an emotional response.

Some authors have studied the response of animals after ablation of the septal regions. Complete bilateral removal of the septal area of the rat by Brady and Nauta[17,18] and by Tracy and Harrison[19] caused increased emotionality and startle reaction and a decreased aversive behavior response. Contrary to these results is the report of Harrison and Lyon[20] that no significant increase in emotionality resulted from such lesions in the rat (they reported docility in some) and Bond and associates[21] reported changes of emotionality only when the fornix fibers and anterior part of the thalamus were involved in the lesions. There appears to be some question concerning the effects of a bilateral lesion of the septal area. In the present series of experiments, complete bilateral removal was not accomplished in any of the animals. Only 1 animal showed a change in behavior, that of a slight hyperkinesia. However, this same animal had a portion of the frontal lobe removed on both sides as well, and thus no definite conclusion can be drawn. Possibly lesions must be large enough to include more than just septal connections to cause a visible effect, or, perhaps, the testing methods used were not of a sufficiently precise nature to determine minor defects that may have been present.

A review of the connections of the septal areas is obtainable in the text by Kappers, Huber, and Crosby.[22] Since the publication of this text, further morphologic descriptions of

the connections of this area have appeared in the studies of Wallenberg[23] on the guinea pig, Young[24] on the rabbit, Fox[25] on the cat, and, of special importance for this study, Lauer[1] on the monkey. It is evident from these reports that the septal nuclei receive connections from the olfactory bulb, frontal cortex, and amygdaloid nuclei; that they are interconnected with the olfactory tubercle, hippocampus, dorsal thalamus, hypothalamus (the last connection by way of either the medial forebrain bundle or the postcommissural column of the fornix), and diagonal band of Broca; and that they send efferent fibers to the habenula. All the nuclei of the septal region are richly interconnected. Although the material used in this series of experiments is insufficient to confirm many of these connections, certainly some of them are implied and there is no evidence to suggest that any of these connections do not exist.

As early as 1917, Crosby,[26] studying Golgi material of the alligator forebrain, suggested that the lateral septal nucleus is a way station for descending impulses coming from the hippocampus and that the medial septal nucleus has a similar relation to ascending impulses going to the hippocampus. Loo,[27] Young,[24] Fox,[25] and Lauer[1] have all made similar suggestions from the study of normal material of the opossum, rabbit, cat, and monkey, respectively. It should be emphasized that these conclusions were made from normal material. However, an unproven assumption has been prevalent that the fornix is purely an efferent bundle of fibers with respect to the hippocampus, containg no afferent hippocampal fibers.

Campbell and Sutin[28] stimulated the fornix of rabbits and cats and noted that this caused electrical responses in the hippocampal pyramidal cells. Similarly, Morin and Green[29] found that stimulation of the fimbria of guinea pigs and cats caused after-discharges over the cerebral cortex and cerebellum. These after-discharges were not eliminated by fornix section. Green, Adey, and Arduini[30–32] have noted that olfactory, visual, auditory, and somesthetic stimulation caused responses of a peculiar "arousal" type in the hippocampus of cats, monkeys, rats, and rabbits. These hippocampal responses were eliminated by removal of the septal areas. They also found that stimulation of the ascending reticular system gave similar hippocampal responses that were also eliminated by septal ablation. The physiologic data very definitely suggest that there are fibers in the fornix, afferent with respect to the hippocampus. Further electrophysiologic studies by Stoll, Ajmone-Marson, and Jasper[33] in the cat and by Cragg and Hamlyn[34] in the rabbit suggest that the septal areas are interconnected with the temporal pole and the subiculum by way of the fornix.

McLardy,[35,36] using retrograde cell degeneration technics, suggested the possibility of septohippocampal fibers in the monkey, since section of the fornix caused a retrograde degeneration of the cells in the medial septal nucleus. Morin,[37] using the Marchi method on the guinea pig, found that lesions of the septal area caused degeneration in the ascending part of the fornix.

The present study strongly suggests that fibers, the cell bodies of which are located in the septal area, course through the fornix to the hippocampus and terminate about the pyramidal cells in this area. It may be remembered that facial movements obtained on stimulation were eliminated when the fornix was cut. This suggests that the impulses travel from the septal area to the hippocampus. Votaw[38] has shown that stimulation of the hippocampus of the macaque causes a type of movement similar to that obtained in these experiments on the septal area. By selective sectioning, he also found that the pathways carrying impulses that mediate these movements are directed to the hippocampal gyrus and the temporal lobe. He indicated the possibility that the impulses were then relayed to the tegmentum of the brain stem by temporotegmental pathways.

From the evidence in the present set of experiments and from a survey of the literature, one may formulate some concept of the possible function of the septal area. Figure 3 will aid in such a formulation. Olfactory impulses certainly reach the septal area. In addition to this afferent supply, most other sensory modalities also project to the septal area, but as nonspecific afferent impulses that have traveled by way of the ascending reticular system. Another major source of afferent

impulses seems to be the frontal lobe, an area known to have some effect on the personality of the individual. Thus, the septal area represents a region in which various sensory impulses are concentrated and probably associated. The efferent discharge of these nuclei, then, represents a balance resulting from all the afferent impulses reaching the area. This discharge is by way of the postcommissural fornix column, the medial forebrain bundles, the diagonal band of Broca, and, of most concern for our purposes, the fornix itself.

It is not unreasonable to assume, since many sensory modalities, including both visceral and somatic, are represented in the septal area, that this region is directly concerned with affective behavior and emotional expression. The impulses that mediate the expressive side of such behavior may travel by way of the fornix to the hippocampus. The hippocampus may regulate emotional expression by responding to the multitude of afferent information that it receives. The septal nuclei represent only one pathway for such afferent impulses, destruction of which will only slightly alter, but certainly not eliminate, hippocampal function. From the hippocampus, impulses reach the temporal lobe and are relayed to the brainstem reticular areas, which then discharge impulses to the motor nuclei of the many peripheral nerves. The septal nuclei thus become an integral part of a neural arc concerned with emotional expression.

CONCLUSIONS

1. This investigation of the septal area of the macaque monkey is based on data from stimulation and ablation experiments. Additional information has been obtained by a study of the degenerated pathways that resulted from the lesions produced.

2. Adequate stimulation of the septal nuclei produces facial and upper extremity movements. There is no consistent pattern of movements represented in the septal area. Cutting the body of the fornix bilaterally eliminates responses obtained from such stimulation.

3. Small lesions of the septal area, even when present on both sides, do not cause any observable changes in the behavior of the animals. There is suggestive evidence that larger lesions of the septal area, which include some destruction of the frontal cortex, produce hyperkinesia.

4. A major efferent tract from the septal area is composed of fibers in the fornix, which are afferent with respect to the hippocampus. Each area distributes mainly to the hippocampus of the same side with a small distribution to the opposite hippocampus.

5. It is suggested that a part of at least one neural arc for emotional expression is represented by a pathway that discharges from the septal nuclei to the hippocampi. An intact hippocampus is necessary for the proper functioning of this arc.

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Cardrase: a new carbonic anhydrase inhibitor

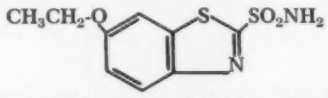
Its use in epilepsy

Sidney Merlis, M.D.

SINCE the initial reports of Bergstrom and associates[1] and Merlis[2] on the use and clinical value of acetazolamide (Diamox), a carbonic anhydrase inhibitor, in the treatment of convulsive disorders, further reports have been published corroborating the usefulness of this class of compound. The present report deals with the effects of a new carbonic anhydrase inhibitor, ethoxzolamide (Cardrase), in the treatment of convulsive disorder.

CHEMICAL DATA

Ethoxzolamide (Cardrase) is a pure white, crystalline solid, odorless and tasteless. Chemically, it is 6-ethoxybenzothiazole-2-sulfonamide, with the structure as follows:



The material is poorly soluble in water, forms soluble salts with alkali, is stable in the solid form, and is nonhygroscopic. It was made available for this study in tablets of 125 mg. and 62.5 mg.

PROCEDURES AND RESULTS

A group of 36 outpatients, consisting of 19 males and 17 females ranging in age from 3 to 59 years, was studied. All were under close observation and had been seen at fairly regular intervals for periods of from two months to four years before Cardrase was put into the therapeutic regime. All had received thorough physical examination and neurologic evaluation including electroencephalograms, as well as complete blood counts.

Base line seizure incidence was established and graded according to arbitrary criteria. Good control was definied as complete absence of seizures or not more than 1 seizure per month. Fair control was indicated in patients averaging 2 to 4 seizures per month. Poorly controlled patients were those having more than 4 seizures per month. All patients utilized in this study had fair to poor seizure control prior to the beginning of this study.

Cardrase was gradually introduced in addition to the previously prescribed therapy. Dosages of the new agent in the early period of this study were gradually increased, so that some of the patients received as much as 750 to 1,000 mg. per day orally in divided doses with meals. As our experience increased, we felt that the anticonvulsant effectiveness of Cardrase did not increase with increased dosage. It was found that effective seizure control was maintained with dosages ranging from 125 to 375 mg. daily. As improvement appeared in some of our patients, efforts were made to decrease some of the previous medication. In almost every instance, a significant decrease in related anticonvulsive medication was associated with an increase in seizure incidence. In only 1 case were we able to achieve adequate seizure control with Cardrase alone. This case was that of a 37-year-old female suffering from grand mal seizures occurring almost entirely just before or during her menses. She was placed on 125 mg. of Cardrase three times a day and has been seizure free for the nineteen months up to the time of this report.

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CARDRASE (Tabulated Results)

Diagnosis	Number	Female	Male	Seizure control*: Before Cardrase Good	Fair	Poor	After Cardrase Good	Fair	Poor
Grand mal	21	9	12		6	15	12	7	2
Petit mal	4	2	2		2	2	3	1	
Grand and petit mal	7	6	1			7	2	3	2
Jacksonian	3		3			3	3		
Akinetic	1		1		1		1		
Total	36	17	19	0	9	27	21	11	4

*Criteria of seizure control:
Good: Complete absence of seizures or not more than 1 seizure per month.
Fair: 2 to 4 seizures per month.
Poor: More than 4 seizures per month

Patients in this series have been observed for varying periods up to twenty-one months. The results are summarized in the table. Of the entire group, 4 patients continued to be poorly controlled even with the addition of Cardrase; 21 achieved good seizure control. None had good control prior to the use of Cardrase; 11 were considered to have fair seizure control, compared to 9 previously.

Side effects were reported by 4 patients. Headaches, feelings of fatigue, mild gastric irritation, and some paresthesias of the perioral area and extremities were noted. It is significant that 1 patient who had previously been unable to tolerate Diamox because of peripheral paresthesia also could not tolerate Cardrase for the same reason. The side effects in the 4 patients could not be related to dosage inasmuch as 1 patient was sensitive to 62.5 mg. of Cardrase daily.

DISCUSSION

Most of the cases used in this study were of the idiopathic type. The numbers of cases in the various categories of seizure types are too small to establish any statistically valid conclusions. Nevertheless, a trend can be established as a result of the present findings. It would appear that Cardrase is effective as an adjunctive aid to be used in addition to other anticonvulsive therapies in the treatment of seizure disturbances. There is evidence that this agent is twice as potent as Diamox, so that one-half the dose usually required for the adjunctive anticonvulsant action of Diamox is needed for similar effects with Cardrase. It does not seem that the carbonic anhydrase inhibitors act in a cumulative manner, inasmuch as increasing the dose of Cardrase above an effective level did not serve to improve seizure control. We were able, in some of our patients, to switch from Cardrase to Diamox in appropriate doses without affecting the seizure incidence. Cardrase, like Diamox, has no significant sedative effect; consequently, patients with low sedation thresholds who were receiving other anticonvulsants were able to tolerate the addition of the carbonic anhydrase inhibitor without difficulty.

The incidence and nature of the side effects encountered were practically identical with Cardrase and Diamox. From our experience to date with these 2 carbonic anhydrase inhibitors, it is our opinion that both have essentially the same action clinically. Published reports of the action of these compounds in epilepsy and various clinical disorders also tend to bear this out.[3–6]

There has been much speculation regarding the physiologic significance of carbonic anhydrase inhibition in epilepsy. With respect to the fundamental causes of seizures, various reports have suggested alterations in enzyme disturbance, cell permeability, electrolyte imbalance, and *p*H changes that may relate to anticonvulsive disorder. As yet, however, the precise physiologic basis of convulsive seizures has not been established. The demonstration that carbonic anhydrase inhibitors are agents with some anticonvulsant effect will give fur-

ther impetus to the study of seizure physiology. As more compounds of this class are introduced, further study may lead to a better understanding of the convulsive disorders.

CONCLUSION

1. A new carbonic anhydrase inhibitor, Cardrase (ethoxzolamide), was administered to 36 outpatients with convulsive disorder of various types.

2. When Cardrase was added to the existing medication, significant improvement was achieved in 21 of the 36 patients.

3. The side effects, mode of action, and physiologic activity indicate that Cardrase behaves essentially the same as Diamox, although the former has twice the potency. Both compounds are essentially interchangeable at appropriate dose levels without deleterious effects to the patient.

4. The primary significance of the carbonic anhydrase inhibitors in epilepsy, while of admitted therapeutic value, lies in the fact that compounds of this class perhaps eventually will lead to further data that will help us to understand the pathophysiology of the convulsive state.

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Cardrase was supplied through the courtesy of the Upjohn Company, Kalamazoo, Mich.

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Some aspects of tricarboxylic acid cycle metabolism in the central nervous system

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THE central nervous system is delineated by certain biochemical characteristics that reflect its unique function. The system, representing but 2% of the total body weight of the mammalian organism, is nonetheless responsible for 20% of the basal metabolism, 25% of the total oxygen consumption, and 15 to 20% of the total cardiac output.[1] Under normal conditions, glucose forms the main oxidizable substrate of the central nervous system.[2–4] Fatty acids and acetate are oxidized only slightly, whether in vivo or in vitro.[2,5,6] Glutamine is the only other major carbon source demonstrated to enter the intact central nervous system, although in insufficient amounts for energy requirements.[7] Further, there is little evidence of an active hexose monophosphate pathway in the central nervous system,[8] nor is there evidence of metabolic response to any hormonal substance. The relatively low levels of carbohydrate reserves, that is, glycogen, cannot long maintain the normal metabolic activity of neural tissue.

The chief energy source for the central nervous system is therefore blood glucose, which is degraded to pyruvate by the glycolytic pathway and to carbon dioxide and water by the tricarboxylic acid (TCA) cycle. Pyruvate can enter the TCA cycle in either of 2 distinct routes, by oxidative decarboxylation to acetyl coenzyme A (CoA) or by condensation with carbon dioxide to form a dicarboxylic acid. Pyruvate entering the TCA cycle as acetyl-CoA is coupled to the synthesis of high energy phosphate but does not produce a net gain in dicarboxylic acids. Alternatively, formation of dicarboxylic acids by carbon dioxide fixation results in a net increase in the mass of TCA cycle intermediates, that is, synthetic intermediates are formed, but there is no direct formation of high energy phosphates. The TCA cycle of the central nervous system has been studied by administration of labeled pyruvate or, more precisely, its metabolic equivalent, DL-alanine-2C^{14}, to rats and determination of the relative radioactivity of the individual carbon atoms of L-glutamate, (equivalent to alpha-ketoglutamic acid of the TCA cycle), isolated from central nervous system tissues.

EXPERIMENTS

Adult Sprague-Dawley rats weighing 400 to 500 gm. were used. Animal groups BSH and BFH were gradually acclimatized in a pressure chamber over a period of four weeks to an altitude of 6,600 meters, equivalent to barometric pressure of 321 mm. Hg or oxygen concentration of 8.5%. Animals were maintained at this level for two weeks before use. Only animals that were successfully acclimatized, that is, without weight loss or other physical abnormalities, were utilized. Animal groups BSH and BSA were starved forty-eight hours before administration of isotope. Animal groups BFH and BFA were fed ad libitum and given 2.5 gm. glucose by gastric intubation thirty minutes before injection. No anesthetic agents were utilized. A dose of 5 mg. of DL-alanine-2C^{14}, 0.1 mc., was administered by

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TABLE 1
RELATIVE RADIOACTIVITY OF THE INDIVIDUAL CARBONS OF CNS GLUTAMATE

Carbon number	*BFA**	*BFH**	*BSA**	*BSH**
I	26.0%	24.1%	21.4%	17.0%
II	4.2	3.3	5.7	13.4
III	7.4	8.7	11.3	8.8
IV	18.5	18.3	18.0	15.0
V	39.2	40.2	34.9	40.8
Sum	95.3	94.6	91.3	95.4

$$\text{Percentage activity} = \frac{\text{activity of individual carbon} \times 100}{\text{activity of total combustion} \times 5}$$

*Pool of 3 brains

intracardiac injection to each animal. All procedures and manipulations before sacrifice of the acclimatized groups were performed in secondary chambers at 8.5% oxygen tension maintained by nitrogen dilution.

All groups were killed by decapitation one hour after administration of isotope; central nervous system tissues were removed, mechanically homogenized, and hydrolyzed. L-glutamic acid was isolated and degraded according to previously described procedures.[9]

RESULTS AND DISCUSSION

The theoretic distribution of isotope in TCA intermediates after introduction of radioactive compounds has been discussed in a prior communication.[9] These theoretic patterns correspond quite well to those determined experimentally in the isolated glutamate of various microbiologic and animal systems after administration of radioisotopic intermediates.[10–18] The principal labeling patterns of glutamate carbons may be summarized as follows:

Carbon V of glutamate is labeled as a result of conversion of pyruvate-$2C^{14}$ (the deaminated product of alanine-$2C^{14}$) to acetyl-$1C^{14}$CoA by decarboxylation.

Carbons III and I become radioactive as a result of the conversion of pyruvate to dicarboxylic acids by carbon dioxide fixation.

Carbon I is labeled by both mechanisms.

The Carbon IV label indicates the formation of acetyl-$2C^{14}$CoA by a mechanism to be discussed further.

The data indicate (Table 2) that 55 to 65% of the total radioactivity of glutamate derived from the central nervous system occurred in Carbons V and I in ratios approaching 2:1. Therefore, the major portion of the administered isotope must have been converted to acetyl-$1C^{14}$CoA, entering the TCA cycle for degradation to carbon dioxide and water and not for synthesis of TCA intermediates. Carbon IV, representing 15 to 18% of the total glutamate activity, indicates considerable formation of acetyl-$2C^{14}$ or acetyl-$1,2C^{14}$CoA.

The possibility that Carbon IV might become radioactive as a result of the formation of acetyl-$1,2C^{14}$CoA by carboxylation of pyruvate-$2C^{14}$ followed by 2 sequential decarboxylations is not consistent with the distribution of radioactivity found. Carboxylation of pyruvate-$2C^{14}$ would yield equally labeled malate-$2,3C^{14}$. The radioisotope content of Carbon II of acetyl, and, hence, Carbon IV of glutamate, should not exceed that of Carbon III of malate under such a mechanism. Carbons IV, III, and II of glutamate would be expected to approach identical isotope concentrations, but Carbon IV could not exceed the radioactivity of Carbons III and II. These expectations vary with experimental data.

Reductive cleavage of succinate-$2,3C^{14}$ to form acetyl-$2C^{14}$ could conceivably introduce radioactivity into the noncarboxyl carbons of central nervous system glutamate. Although such cleavage has been observed in several systems, its quantitative significance in mammalian tissues is doubtful.

Hexose monophosphate reactions might result in formation of acetyl-$2C^{14}$CoA and Carbon IV of glutamate. As previously noted, however, available evidence indicates but little shunt activity in the central nervous system.

The formation of glutamate-$4C^{14}$ elsewhere

TABLE 2
COMPARISON OF RADIOACTIVITIES OF INDIVIDUAL CARBON ATOMS OF LIVER AND CENTRAL NERVOUS SYSTEM GLUTAMATE

Carbon number	*Brain, fed*	*Liver, fed*[9]	*Brain, starved*	*Liver, starved*[9]
I	26.0%	15.3%	21.4%	7.7%
II	4.2	18.1	5.7	27.5
III	7.4	40.7	11.3	36.3
IV	18.5	1.1	18.0	0.8
V	39.2	20.3	34.9	3.1
Sum	95.3	95.5	91.3	95.4

in the body and its subsequent assimilation by the central nervous system could also possibly account for the labels in Carbons I, II, III, and IV of central nervous system glutamate. Such formation and transport would take time and would involve considerable dilution. The strongest objection to this mechanism, however, is that the labeling pattern of glutamate obtained from the livers of similar experimental animals (Table 2) is not the same as that in central nervous system glutamate, and, indeed, Carbon IV of liver glutamate was hardly labeled at all. Even though an influx of glutamate from the liver into the central nervous system via the blood stream might serve to modify the ultimate labeling pattern of central nervous system glutamate, any significant input would tend to alter the pattern of central nervous system glutamate to approximate that of liver; the patterns would approach identity with time. The dissimilarity of the patterns of liver and central nervous system glutamate tends to minimize the probability that blood-transported glutamine is significant in the production of radioactivity in Carbon IV of central nervous system glutamate.

Carbon metabolism as a source of radioactivity of Carbon IV of central nervous system glutamate is suggested by the labeling pattern derived from administration of formate-C^{14} to rats, where a relatively large proportion of radioactivity was found in Carbon IV of isolated glutamate.[18] Relatively large amounts of serine, glycine, ethanolamine, and choline are found in the central nervous system. If synthesis occurs in situ, an active carbon metabolism is implied. The principal source of glycine in animals is serine,[19] which in turn is derived from 3-carbon intermediates of glycolysis.[20] Glyoxalate might act as either a precursor or a product of glycine and might be catabolized to carbon dioxide and formate by formation of a Schiff base between glyoxalate and glutamate.[21] Glyoxylic acid oxidase, in the presence of diphosphopyridine nucleotide, converts the Schiff base to N-formyl glutamic acid and carbon dioxide. N-formyl glutamate is in reversible equilibrium with N_{10}-formyl-tetrahydro-folic acid and glutamate.[22] These mechanisms constitute the pathway for the alpha carbon of glycine to form the beta carbon of serine, potentially a source of the alpha carbon of acetyl. The rapidity of the serine-glycine interconversion permits pyruvate-$2C^{14}$ to act as a source of glycine-$2C^{14}$, serine-$2C^{14}$, formate-C^{14}, and acetate-$2C^{14}$, all capable of labeling Carbon II of acetyl-CoA.[18,23] In addition, there is close similarity in the labeling patterns of isolated glutamate obtained on administration of formate-C^{14}, pyruvate-$3C^{14}$, glycerol-1,$3C^{14}$, or serine-$3C^{14}$, all potential sources of acetyl-$2C^{14}$CoA.[18] Experimentally administered pyruvate-$2C^{14}$ has resulted in glycine-$2C^{14}$, which in turn yielded totally labeled aspartate,[24,25] supporting the hypothesis.

The data also demonstrate that the central nervous system glutamate labeling patterns were not significantly altered in response to alterations of 2 environmental circumstances, acclimatized hypoxia and starvation. This invariance contrasts sharply with the situation in liver, where metabolic events were affected by the same environmental parameters.[9]

Apparently, the central nervous system, a hormonally unresponsive organ, is metabolically oriented toward the maintenance of a constant level of synthesis and energy production with but little margin for variation. It is also apparent that the central nervous system actively catabolizes both acetyl-CoA and dicarboxylic acids, but experimental data provide evidence of but little synthesis of TCA cycle intermediates. The central nervous system seems, therefore, to depend largely on peripheral sources for both glucose and dicarboxylic acids. It is not improbable that the availability of glutamine is rate limiting. The central nervous system, in contrast to hormonally responsive organs, attempts to maintain a relatively constant level of synthesis and energy production as required by its functional activity. Glutamine, as a major peripheral source of TCA cycle intermediates, is perhaps the key intermediate in the maintenance of metabolic homeostasis.

It is postulated that [1] a highly active carbon metabolism exists in the central nervous system; [2] the central nervous system is dependent upon the peripheral organs for both glucose and dicarboxylic acids; and [3] there is no direct metabolic response of the central nervous system to acclimatized hypoxia or starvation.

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Cerebellar hemorrhage

A clinicopathologic study

J. Rey-Bellet, M.D.

ALTHOUGH isolated cases of hemorrhage in the cerebellum have been reported during the past century, there have been only few studies of relatively large series.[1–4] Attempts at delineating a syndrome in order to make a diagnosis during the patient's life have not been very successful. The affection is not mentioned, or only cursorily treated, in most textbooks of neurology.

Since the frequency of this disorder appears to warrant more attention than it has received, the cases seen at the Pathology Department of Bellevue Hospital between 1938 and 1955 have been reviewed. In a total of 4,526 autopsies in which the head was examined, there were 204 cases of intracerebral and 20 of intracerebellar hemorrhage (Table 1). The incidence of intracerebellar hemorrhage was about 1 in 206 autopsies. Since none of the cases was obtained from the Medical Examiner's Office, these figures represent the actual incidence of the disease in a general hospital. Figures reported by previous authors vary between 1 case in 1,726 autopsies[1] to 1 in 258.[4] The proportion of cerebellar to cerebral hemorrhage also presents wide variations in the published series, between 1%[1] and 15%.[4]

TABLE 1
INCIDENCE OF CEREBRAL AND CEREBELLAR HEMORRHAGES

Autopsies with examination of the head	4,526	
Cerebral hemorrhages	204	4. 5%
Cerebellar hemorrhages	20	0.44%
Proportion of cerebellar to cerebral hemorrhages	1/10.2	(9.8%)

TABLE 2
TYPES OF ONSET IN 21 CASES OF CEREBELLAR HEMORRHAGE

Coma preceded by subjective symptoms	6
Coma without premonitory symptoms	5
Stuporous state preceded by subjective symptoms	4
Stuporous state without premonitory symptoms	3
Subjective and/or cerebellar symptoms	2
Collapse followed by return of consciousness	1
Total	21

CLINICAL MANIFESTATIONS

The patients ranged in age from 43 to 75 years; 7 patients were in the fifth decade, 4 in the sixth, 7 in the seventh, and 2 in the eighth. In 1, the age was not stated. There were 11 males and 10 females.

Symptoms. Onset was frequently dramatic (Table 2); 5 patients went suddenly into coma, without any premonitory symptom. In 6, coma was preceded by nausea, vomiting, dizziness, profuse sweating, and frontal or occipital headaches, lasting usually one or two hours but at times only a few seconds. The loss of consciousness was not always immediately complete; 7 patients went into a stuporous state that gradually deepened into coma over a period of a few hours, and 4 of these complained of nausea, vomiting, dizziness, and headaches immediately preceding onset of stupor. Another patient suddenly collapsed in the street, to regain consciousness in a few minutes. In 1 patient, the initial symptoms were more suggestive of a cerebellar lesion, consisting of an episode of vomiting, lasting a few hours, followed by unsteady gait persisting until admission four days later. The initial symptoms in another consisted of weakness, nausea, vomiting, cold perspiration, and dizziness with mild chest pain lasting only a few

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TABLE 3
FREQUENCY OF SYMPTOMS IN 21 CASES OF CEREBELLAR HEMORRHAGE

Impaired consciousness	18
Nausea, vomiting	9
Headaches	8
Dizziness	7
Profuse sweating	3
Dysarthria	2
Collapse	1
Cerebellar symptoms	1

hours, without any clouding of consciousness. The frequency of the various symptoms is given in Table 3.

History of intermittent symptoms prior to onset of final illness was elicited in 5 patients. These consisted of dizzy spells, sensation of general weakness and mental dullness, ill-defined malaise, and blurred vision.

Signs. Common findings on examination were impairment of consciousness, pupillary abnormalities, respiratory disturbances, evidence of unilateral or bilateral pyramidal involvement, and disorders of ocular movements. Generalized flaccidity and cerebellar signs were found less frequently (Table 4).

Impairment of consciousness. When seen for the first time, 11 patients were in coma and 7, stuporous; only 3 were perfectly conscious. When other symptoms also had been present, coma or stuporous state occurred in less than six hours in the majority of patients. Eventually, all patients lapsed into coma and remained in this condition until death; fluctuation in the state of consciousness was not observed. Death occurred less than twelve hours after onset of complete unresponsiveness in 8 patients, in twelve to twenty-four hours in 7, and in one to three days in 6.

TABLE 4
FREQUENCY OF SIGNS IN 21 CASES OF CEREBELLAR HEMORRHAGE

Coma or stupor	18
Pupillary abnormalities	15
Respiratory disturbances	14
Disorders of ocular movements	10
Pyramidal involvement	10
Generalized flaccidity	7
Absent corneal reflexes	7
Cerebellar signs	2
Blood in the spinal fluid (17 cases)	17

Pupillary abnormalities were the next most common findings, being present in 15 patients. The pupils were normal in 5; their condition was not recorded in 1. Pinpoint pupils were found in 10 patients and unequal pupils in 3. In 2, there was no reaction to light.

Respiratory disturbances were present in 14 patients. Of these, 4 had deep, stertorous breathing, 3 were in Cheyne-Stokes, 1 was gasping and cyanotic, and another had rapid and shallow respiratory movements that ceased altogether with slowing of the heart rhythm to 20 to 40 beats per minute. Marked respiratory disturbances were not always signs of impending death, 2 patients remaining in Cheyne-Stokes for thirty-six hours before death; 1 patient developed sudden pulmonary edema and died a few minutes later. Another had laryngeal spasm that necessitated tracheotomy and died twenty-four hours later. In the terminal period, 4 patients had what appeared to be a sudden depression of the respiratory center; they stopped breathing, while pulse and heart sounds continued to be strong. They were maintained alive with artificial respiration for a period of time varying from two and one-half to twenty-two hours.

Abnormal ocular movements were observed in 10 patients. In 3, the eyes were fixed forward and no motion could be elicited. There was conjugate deviation of the eyes in 2 patients; both were stuporous, and the deviation disappeared at the onset of complete coma. Ptosis of the eyelids was present in 2 cases; 1 patient had nystagmus and 1, paralysis of convergence. In 1, the eyes were deviated downward and motionless. Oculomotor paralysis was not observed.

Pyramidal involvement. Evidence of unilateral or bilateral pyramidal involvement was found in 13 patients. However, when signs that might be due to another cerebral lesion were excluded, those that can be attributed to the cerebellar hemorrhage or its complications were hemiplegia in 4 cases, hemiplegia with extensor plantar reflex on the opposite side in 3, and Babinski sign alone in 3.

Corneal reflexes were absent bilaterally in 5 patients, all of whom were in coma; they

disappeared in 2 only in the terminal stage, when the pinpoint pupils became dilated. In 2 patients, the corneal reflex was absent on 1 side and weak on the other; both were also in coma.

Flaccidity. Generalized flaccidity was observed in 7 patients; 3 had evidence of bilateral pyramidal lesion, 2 later had hemiplegia, and 2 had no evidence of pyramidal tract involvement.

"Cerebellar" signs were found in only 2 patients; 1 had truncal ataxia and the other, slurred speech and nystagmus. He also complained of vertigo and blurred vision. Of more doubtful significance was a coarse tremor of the left upper extremity in a patient with old left hemiplegia. This low incidence of objective evidence of cerebellar dysfunction may be partly due to the fact that most patients had impaired consciousness. However, 2 mentally clear patients failed to show any disturbance of equilibrium or coordination.

Blood pressure. All but 3 patients had elevated blood pressure on admission; 1 was in shock and 2 in cardiac failure with high diastolic and low systolic pressure. If the patients in shock and cardiac failure are excluded, the values for blood pressure ranged from 130/80 to 270/170. Systolic pressure was 200 mm. Hg or more in 8 patients and less than 200 in 10, the average being 198. Diastolic pressure was less than 100 in only 4 patients, the average being 117.

Laboratory findings. Lumbar puncture was performed in 17 patients; 14 had grossly bloody cerebrospinal fluid, and 3 had only a few red blood cells, 1 of them with xanthochromic supernatant fluid. Only 3 had nuchal rigidity. Other laboratory examinations were not helpful for the diagnosis; 4 patients had glycosuria, 2 of whom had slightly elevated fasting blood sugar, 10 had albuminuria, and 1 had acetonuria. Leukocytosis that could not be explained by an inflammatory process was present in 2 patients.

Course. The patients' conditions deteriorated rapidly, 5 of them dying within the first twelve hours and 5 others in less than twenty-four hours; 8 died one to three days after onset, and 3 survived five, six and seven days, respectively. The shortest interval between onset and death was eighty minutes.

TABLE 5
LOCATION OF LESION IN 21 CASES OF CEREBELLAR HEMORRHAGE

Left hemisphere	8
Right hemisphere	4
Both hemispheres	6
Vermis and left hemisphere	2
Vermis and both hemispheres	1
Total	21

No precipitating factors could be found in the majority of the cases; 15 patients were known to have been hypertensive for one or several years, 2 of them being in cardiac decompensation and 2 presenting symptoms of coronary insufficiency, 10 were obese, 3 were alcoholic, 1 had central nervous system syphilis, 1 was diabetic, and 8 had a history and/or anatomopathologic evidence of previous cerebrovascular disease.

The final clinical diagnosis was cerebral hemorrhage in 10 patients, primary subarachnoid hemorrhage in 4, cerebral thrombosis in 2 and pontine hemorrhage in 2. In 3 cases, diagnoses of pneumococcal meningitis, thrombocytopenic purpura, and uremia were made, respectively, no additional cerebral pathology being suspected.

PATHOLOGY

Location of the hemorrhages is given in Table 5. As can be seen, there was bilateral although unequal involvement in 7 of the 21 cases. In 14 cases, the hemorrhage was very extensive, destroying more than half of one cerebellar hemisphere; in 4, a small hemorrhage was found, not exceeding 2 cm. in diameter, and in 3, the size was not recorded.

In only 3 instances was the hemorrhage limited to the cerebellum itself. In 7, it had ruptured into the fourth ventricle (with secondary spread to the subarachnoid space through the foramina of Luschka and Magendie), in 6 directly into the subarachnoid space, and in 5 additional cases, in both. Thus, in 18 of the 21 cases, there was blood in the subarachnoid space; 2 patients also had blood in the subdural space.

Associated lesions were frequently found in the brain stem or cerebral hemispheres; 1 case showed hemorrhage in the tegmentum of

the upper midbrain on the right, which increased in size and extended bilaterally into the lower midbrain. Another had hemorrhage around the aqueduct of Sylvius and in the substantia nigra on the right. Another patient had thrombosis of the basilar artery with anemic infarct of the pons.

Old infarcts in the cerebral hemispheres were seen in 8 cases, but none were of recent date or thought to be a sufficient explanation for the clinical symptoms; 1 patient had a small hemorrhage in the left occipital pole and a hemorrhagic infarct in the right internal capsule, both of recent origin.

Incidental findings were a pituitary chromophobe adenoma and lateral sclerosis of the spinal cord.

Cerebellar hemorrhage had caused additional intracranial pathology in 9 patients; 7 had flattening of the convolutions with some degree of ventricular dilation, all but 1 having intraventricular hemorrhage, and 3 presented a pressure cone with herniation of the cerebellar tonsils.

A severe degree of arteriosclerosis in the vessels of the base was seen in 10 cases. In 5, the arteriosclerosis was moderate and in 5, slight; 1 patient had normal vessels.

Evidence of arteriosclerosis in other parts of the body was present in 18 cases; 9 had coronary arteriosclerosis, 2 with old myocardial infarcts. The heart was definitely enlarged in 19 of the 21 cases, weighing from 390 to 800 gm.; average weight was 478 gm.

ETIOLOGY

On the basis of clinical and anatomic data, hemorrhage was attributed to hypertension with arteriosclerosis in 17 cases and to arteriosclerosis alone in 1. In 1 of the 3 remaining cases, the cause was thrombocytopenic purpura of unknown etiology; in another, a hemorrhagic syndrome with involvement of the adrenals followed pneumococcal meningitis, and, in the third, the cause was craniocerebral injury with concomitant skull fracture.

CLINICOPATHOLOGIC CORRELATIONS

Most of the symptoms and signs observed in this series of patients cannot be explained on the basis of loss of cerebellar tissue alone and point rather to brain stem dysfunction. Since, in the majority of the patients, no anatomic changes were found in the pons or midbrain, it may be assumed that there was compression, edema, and/or disturbance of the vascular supply; 3 of the patients had softening or hemorrhage in the brain stem but, clinically, did not differ significantly from the cases without such lesions.

In the cases with unilateral pyramidal involvement, the peripheral signs were on the side of the cerebellar lesion in 2 and on the opposite side in 5. In the 3 cases with hemiplegia on 1 side and extensor plantar reflex on the other, the cerebellar lesion was homolateral to the hemiplegia in 2 and contralateral in 1.

In the 5 patients with pupillary inequality, the larger pupil was on the side opposite the hemisphere containing the hemorrhage. When the corneal reflex was absent on one side only, that side was ipsilateral to the cerebellar lesion.

The one instance of truncal ataxia occurred in a patient having a hemorrhage in the vermis. No incoordination, dysmetria, or tremor of the extremities was elicited by the usual finger-nose and heel-knee tests. Deviation of the head and eyes is said to occur in cerebellar lesions, the deviation being toward the affected side;[5] 2 patients had deviation of the head and eyes or of the eyes only, both toward the right and both having a left cerebellar hemorrhage. Coarse tremor of the left upper extremity was present in 1 instance; no lesion was visible in the midbrain, and the red nucleus was normal, but an old infarct was present in the left caudate nucleus. The hemorrhage was located in the left cerebellar hemisphere.

Intraventricular inundation occurred only in cases with extensive hemorrhages; it was present in 9 of the hemorrhages classified as large and absent in 5. It was not found in the 4 patients with small hemorrhages. The duration of life was not appreciably different in the group with (12 cases, average forty-seven hours) or without (9 cases, average forty-five hours) blood in the ventricular system. The initial state of consciousness of the patients appears to be related to the presence of blood in the ventricular system. This was found less frequently in the patients who were conscious or stuporous when first seen than in those admitted in coma.

TABLE 6
REVIEW OF 4 SERIES OF CEREBELLAR HEMORRHAGE

Author	*Michael*[1]	*Hyland*[2]	*Friedman*[7]	*Present series*	*Total*
*Number of cases**	4	30	3	21	58
Duration of life					
Less than 24 hours	1	14	2	10	27
More than 24 hours	3	16	1	11	31
Symptoms					
Impaired consciousness	4	9	3	18	34
Headaches	4	17	–	8	29
Nausea, vomiting	3	11	1	9	24
Dizziness	1	6	1	7	15
Cerebellar symptoms	–	5	1	1	7
Signs					
Disturbance of consciousness	3	22	3	18	46
Respiratory disturbances	3	15	2	14	34
Pupillary changes	2	12	3	15	32
Pyramidal signs	3	14	2	10	29
Disorders of ocular movements	2	8	1	10	21
Cerebellar signs	–	6	–	2	8
Blood in cerebrospinal fluid**	3(3)	12(14)	1(1)	17(17)	33(35)

* Only cases for which sufficient clinical information is available are included.
** Figures in parentheses indicate number of cases in which lumbar puncture has been performed.

The size of the hemorrhage itself was not always the most important factor in the evolution of the disease or its clinical manifestations. Cases with small hemorrhages survived on the average slightly longer than those with larger ones, but there was a wide variation within each group.

DISCUSSION

Cerebellar hemorrhage is classicaly considered a rare and fatal disease,[4,6] the diagnosis very rarely being made during life. However, our figures, as well as those of others,[2–4] indicate that its frequency is greater than is generally thought.

The main symptoms of the disease are headaches, nausea, vomiting, and dizziness, followed more or less rapidly by loss of consciousness. At examination, pupillary changes and respiratory disturbances are the most common findings. Evidence of pyramidal tract involvement and disturbance of the oculomotor system of the "supranuclear" type are also frequently encountered. Cerebellar signs are found in very few cases. The course is rapid, coma becoming gradually deeper and death occurring within a few days. Table 6 summarizes the clinical picture in 3 previously reported series and the present study.

Cerebellar hemorrhage is distinguished from pontine hemorrhage and infarction by the absence of cranial nerve palsies and, in most cases, of bilateral pyramidal tract involvement. Hemorrhages in both locations have a sudden onset, although it is somewhat more abrupt and the course more rapidly fatal in pontine lesions. Brain stem infarctions have a more protracted and fluctuating course; the cerebrospinal fluid contains no blood.

Cerebral infarction does not, as a rule, produce pupillary and oculomotor disturbances; signs are more strictly unilateral, coma is less profound, and courses slower. The absence of blood in the cerebrospinal fluid will also help in differentiating between the 2 conditions.

Cerebellar hemorrhage is most likely to be confused with hemorrhage in the cerebral hemispheres. In both, pupillary abnormalities, bloody cerebrospinal fluid, occasional bilateral Babinski sign, and rapid course are present. The only points that may help in differential diagnosis are the greater frequency in cerebellar hemorrhage of headaches, nausea, vomiting, and dizziness before onset of unconscious-

ness; more gradual onset of coma; disorders of ocular movements; and, in rare instances, evidence of cerebellar dysfunction. Coma is less deep, at least in the initial stage. In cerebellar hemorrhage, the pupils are often constricted, whereas they tend to be fixed but of medium size or dilated when the cerebral hemispheres are involved. However, in the present state of our knowledge, if a cerebellar location can be suspected, it cannot, except in rare cases, be confirmed with any degree of certainty. Perhaps, careful attention to the nature of the coma and to signs of brain stem involvement will reveal more reliable diagnostic signs.

Diagnosis of cerebellar hemorrhage has too rarely been made during the patient's life to permit a study of the natural history of the disease. Probably, some cases survive; 2 of our cases, for instance, seem to have died not from the hemorrhage itself but from a complication (intraventricular hemorrhage) or an additional lesion (midbrain hemorrhage). Until more knowledge is acquired on the spontaneous course, it is difficult to evaluate the benefit of surgical intervention.[7-9]

SUMMARY

The clinical and pathologic features of 21 cases of cerebellar hemorrhage are reviewed. The hemorrhage occurred in any part of the cerebellum and usually spread to the subarachnoid and/or ventricular spaces. Occasionally, concomitant brain stem lesions were found.

All of the patients were past middle age. The commonest cause was hypertension with arteriosclerosis. Onset was sudden in most instances, with coma and stupor, at times preceded by nausea, vomiting, dizziness, or headaches.

The most common of the objective findings were pupillary abnormalities, respiratory disturbances, defects in ocular movements, and signs of pyramidal involvement. Incoordination was found in only 1 case. Blood was always present in the cerebrospinal fluid. The patients died from one hour to seven days after onset of symptoms. The symptoms observed point to brain stem dysfunction rather than to destruction of cerebellar tissue. An attempt is made to differentiate this condition from other cerebrovascular disorders.

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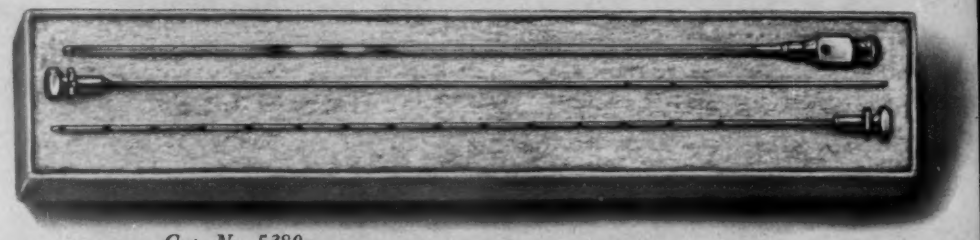

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3. A nylon stylet with radiopaque markings at 1 cm. intervals for indwelling use.

References

*Cooper, I. S.: Chemopallidectomy: An Investigation Technique in Geriatric Parkinsonians, Science 121: 217-218 Feb. 1955.

*Cooper, I. S.: The Neurosurgical Alleviation of Parkinsonism. Springfield, Ill.: Charles C. Thomas, Publisher. 1956.

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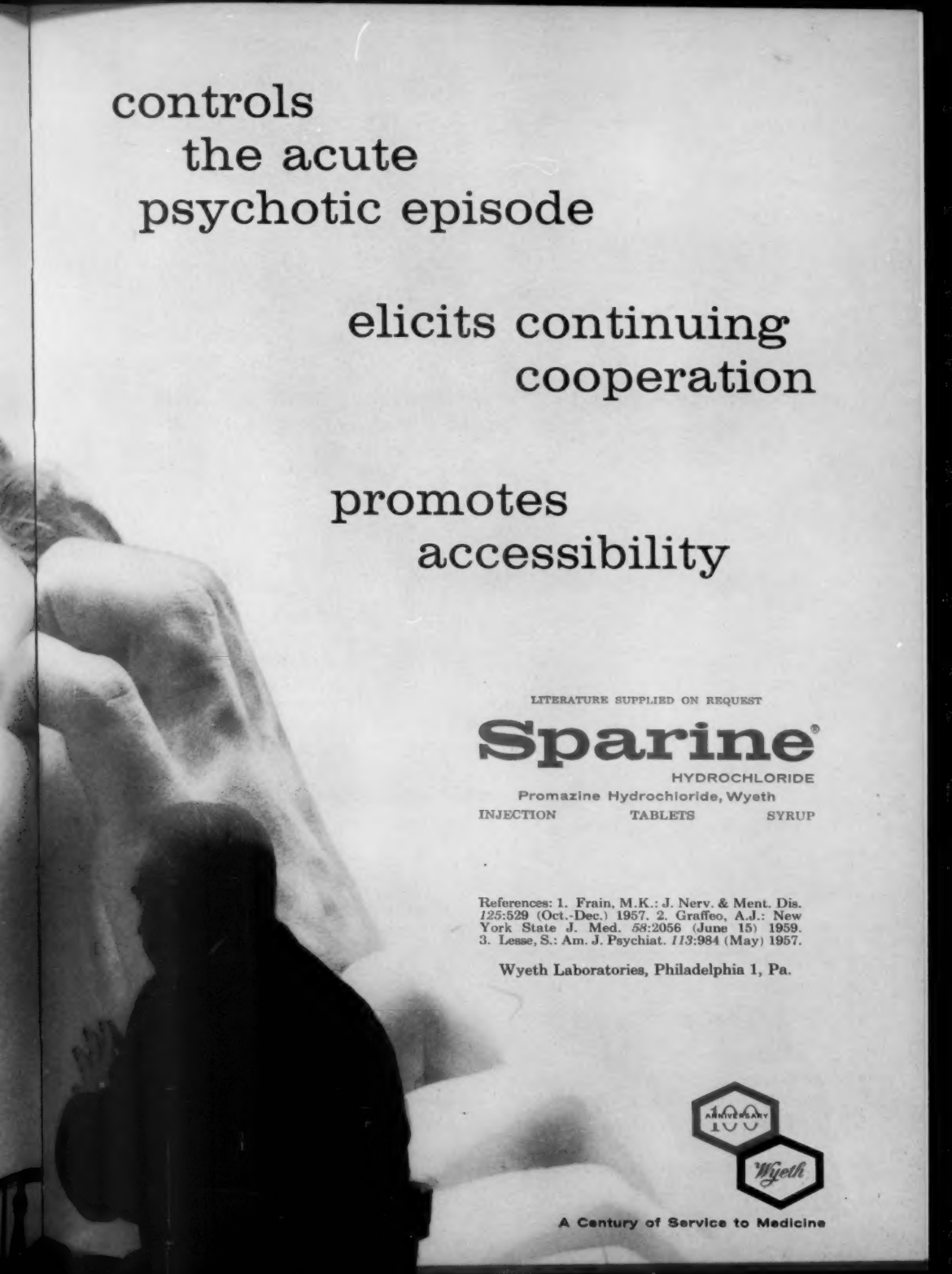

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2. Smith, Richard T.; New York Med. 8:16, 1952.

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

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Joseph M. Foley, M.D., Vice-President
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FEBRUARY 1960

AAN and ANA Appoint Joint International Committee

Augustus S. Rose and Derek Denny-Brown, the respective Presidents of the American Academy of Neurology and the American Neurological Association recently appointed a Joint Committee of the two societies on international representation of American neurology. The Chairman of the new committee, Roland P. Mackay, was appointed jointly and is responsible to both the AAN and the ANA. In addition, three of the committee members, James L. O'Leary, Russell N. DeJong and Joseph Foley represent the AAN, while three other members, Bernard J. Alpers, H. Houston Merritt, and Fred Plum, represent the ANA. The terms of reference of the committee are "responsibility to make recommendations regarding all matters connected with international representation in neurology and, in particular, to make nominations to the two societies of such individuals as may be required to represent American neurology officially at international congresses and at other international meetings."

Philadelphia Neurological Elects Twelve Honorary Members

At its special 75th anniversary meeting (October 23, 1959) the Philadelphia Neurological Society elected as honorary members: Professors Th. Alajouanine, Raymond Garcin, Knud H. Krabbe, G. H. Monrad-Krohn, and H. Olivecrona, Sir Charles Symonds and Sir Francis M. R. Walshe, and Drs. Roland P. Mackay, Byron Stookey, Ludo van Bogaert, I. S. Wechsler, and Gunnar Wohlfart....The Philadelphia Neurological Society, founded in 1883, is the second oldest regional neurological society in the United States....Organized neurology began in the United States with the founding of the New York Neurological Society in 1872. The American Neurological Association was founded in 1875.

Institute for Muscle Disease Formally Dedicated

The dedication exercises for the new Institute for Muscle Disease, a major research arm of the Muscular Dystrophy Associations of America, were formally held in New York on December 12, 1959. An ultramodern structure of steel and glass, erected at a cost in excess of $5,000,000, this new Institute at 515 East 71st Street in New York City will serve as headquarters for the fight against neuromuscular disease. The primary objective of the

Institute is defined in the words of Dr. Ade T. Milhorat, Chairman of the Muscular Dystrophy Medical Advisory Board and Director of the Institute. It is, "to increase our knowledge of muscle, to understand the mechanisms by which muscular dystrophy and other muscular disorders arise, and to develop effective treatments for these conditions." When working at capacity, the Institute will be staffed by approximately 150 scientific workers, and 50 others comprising office staff, maintenance, and housekeeping personnel. The operating budget of the Institute will be approximately $1,500,000 annually. The eleven floors of the building will house several scientific divisions: divisions of Physiology and Biophysics, Enzyme Chemistry and Microbiology, Experimental Pathology, Protein Chemistry, Clinical Investigation, Organic Chemistry, and Biochemistry.

American Epilepsy Federation Formed A total of 26 voluntary epilepsy societies from 13 states have united to form the American Epilepsy Federation. President of the new federation is Mrs. Albert Grass of Quincy, Mass., who, upon assuming the presidency of the new federation stated: "The creation of the American Epilepsy Federation means that at last a concentrated effort to change attitudes and opinions about epilepsy can begin." Among the physicians associated with the Federation are the Vice-Presidents, William G. Lennox of Boston and Harriot Hunter of Denver; Directors-at-Large, Madison Thomas of Salt Lake City; and Academy President, Augustus S. Rose of Los Angeles....Communications should be directed to the American Epilepsy Federation, 77 Reservoir Road, Quincy 70, Mass.

WFN Invites Charter Subscribers to *World Neurology* The World Federation of Neurology has issued an attractive brochure describing the purposes and scope of the new monthly journal, WORLD NEUROLOGY, the official publication of the World Federation of Neurology. The publication date is July 1960. Accompanying the brochure, is a letter from AAN President, Augustus S. Rose, inviting charter subscribers to the journal from those who will receive it from the original issue. The U.S.A. subscription rate is $15 per annum. First editions will be published in limited numbers. Inquiries should be directed to Mr. Allan Stone, Assistant to the Publisher, Lancet Publications, 84 South Tenth Street, Minneapolis 3, Minn.

Tay-Sachs Association Meets in New York Under the direction of its medical Chairman, Dr. S. V. Dunkell, the national Tay-Sachs Association held its annual dinner meeting in the Starlight Roof of New York's Waldorf Astoria Hotel (November 22, 1959). Highlighted on the program was a speech by State Senator Bloom of New York and a paper by Pearce Bailey, "Present Trends in Infantile Neurodegenerative Diseases." The

New York chapter of the national Tay-Sachs Association was formed in 1957 by parents of children suffering from Tay-Sachs disease and the cerebral lipidoses. The Association has established a clinical research program at the Jewish Chronic Disease Hospital of Brooklyn and a basic research program at the Albert Einstein College of Medicine of the Yeshiva University. These programs use a multidisciplinary approach, under the direction of Dr. Bruno Volk, directed to the problem of the cerebral lipidoses.

Bronx VA Hospital Establishes Three-Year Residency Program The Bronx Veterans' Administration Hospital announces the establishment of a three-year approved residency training program in Neurology in affiliation with the Columbia-Presbyterian Medical Center. Besides the regular residency training at the VA Bronx Hospital, residents under this program spend six months full time at the Montefiore Hospital, four months full time in the Department of Neuropathology at the Columbia-Presbyterian Medical Center, and a period in excess of fourteen months attending the various neurologic outpatient clinics of the Neurological Institute of New York. Basic science lectures are given under the aegis of Columbia University. The training program is under the immediate supervision of Carl B. Booth, the neurology chief at the Bronx VA Hospital in collaboration with Daniel Sciarra, Abner Wolf, and Tiffany Lawyer, Jr....Communications should be sent to Dr. Carl B. Booth, Chief, Neurological Section, Veterans' Administration Hospital, 130 West Kingsbridge Road, Bronx 68, New York.

Briefs Paul A. Weiss, Professor and Head of the Department of Developmental Biology at the Rockefeller Institute gave the Fifth Annual Israel S. Wechsler lecture at the Mount Sinai Hospital in New York City (December 11, 1959). His topic was "Problems of Specificity in the Development and Functioning of the Nervous System"....The research committee of the American Academy for Cerebral Palsy, recently appointed by the Academy's president, R. R. Rembolt, is composed of Chester A. Swinyard, Chairman; Pearce Bailey, Webb E. Haymaker, and Horace W. Magoun....Under the auspices of neurophysiology in the department of Neuromedicine of the University of Copenhagen, a nine days' course was given in Electromyography (October 8-17, 1959). The sessions were conducted under the supervision of Fritz Buchthal, Professor of Neurophysiology; Mogens-Fog, Professor of Neuromedicine, and Annelise Rosenfalck, Electronic Engineer. The participants also had the opportunity to practice electromyography on normal subjects and on patients. Seminars were held on the physiologic basis of electromyography and on its clinical applications....The latest national society to join and name a delegate to the World Federation of Neurology is the Association for the Study of Neurology at Malta. The Society's national secretary is Dr. J. Puccicino; its president

and delegate to the WFN is Professor W. Ganado of St. Luke's Hospital in Valetta. The number of nations now members of the WFN through their national societies is 43.

Columbia University Receives Five Million Dollar Donation William Black, President of the Chock Full O'Nuts Corporation and founder and President of the Parkinson's Disease Foundation has given Columbia University $5,000,000 toward the construction of an 18-story medical research building to be located upon the grounds of Columbia's College of Physicians and Surgeons. The donation was described by Dr. Grayson Kirk, President of the University, as the largest contribution ever made by a living person to the 205-year-old institution. The donation will pay about half the cost of the proposed new structure, which contains over 200,000 square feet, and Columbia is to raise the rest. Mr. Black, a member of the class of 1920 at Columbia, made the gift with the hope that it would help solve the medical mystery of Parkinson's disease....H. Houston Merritt, Dean of the College of Physicians and Surgeons and Director of the Neurological Institute of New York, said these new research facilities will enable medical laboratory teams to leave "woefully overcrowded" space for the new building.

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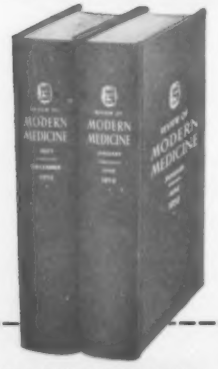

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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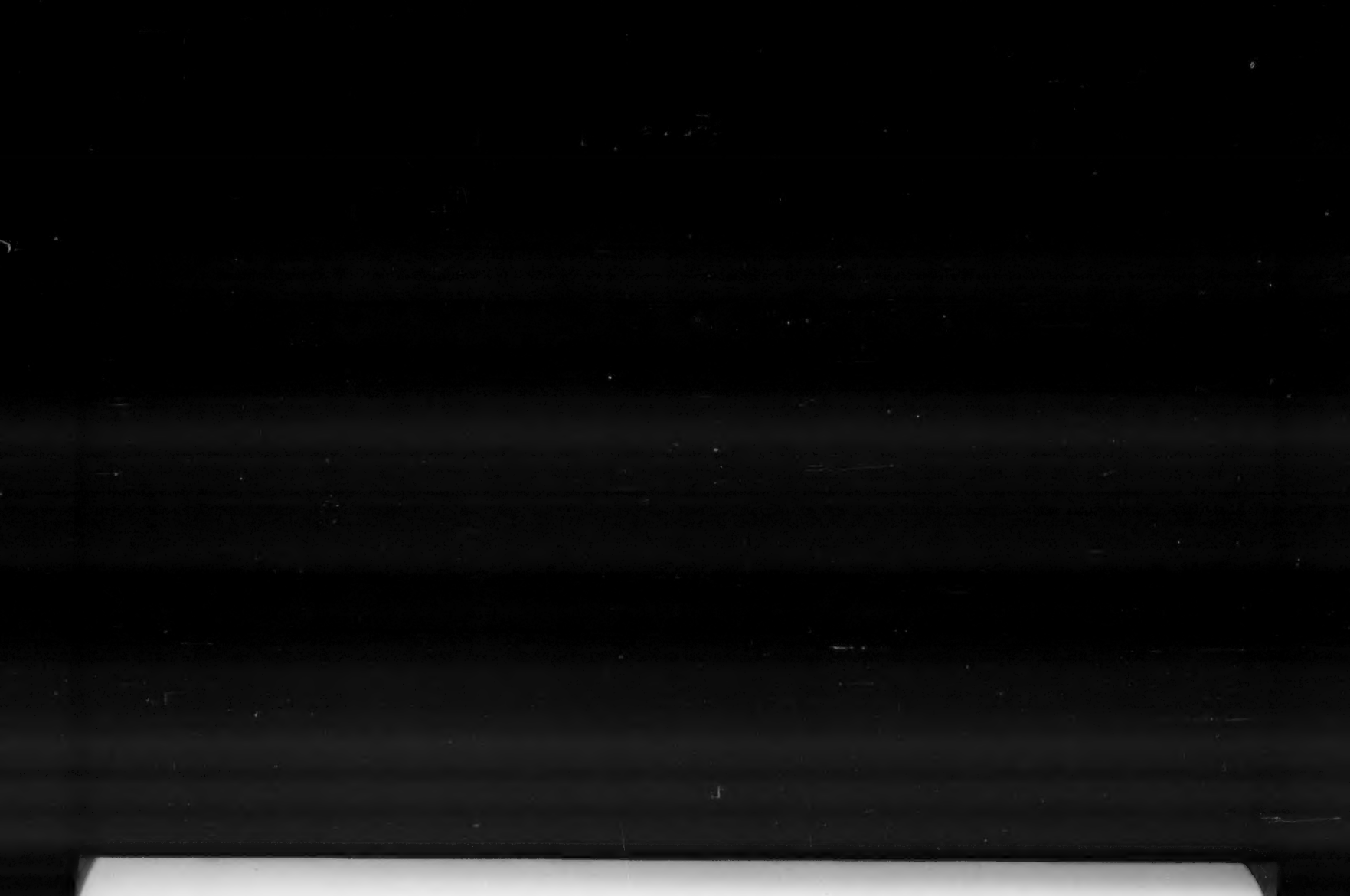
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